# THE Journal Kansas Medical Society

AUGUST
1957

VOL LVIII
NO VIII

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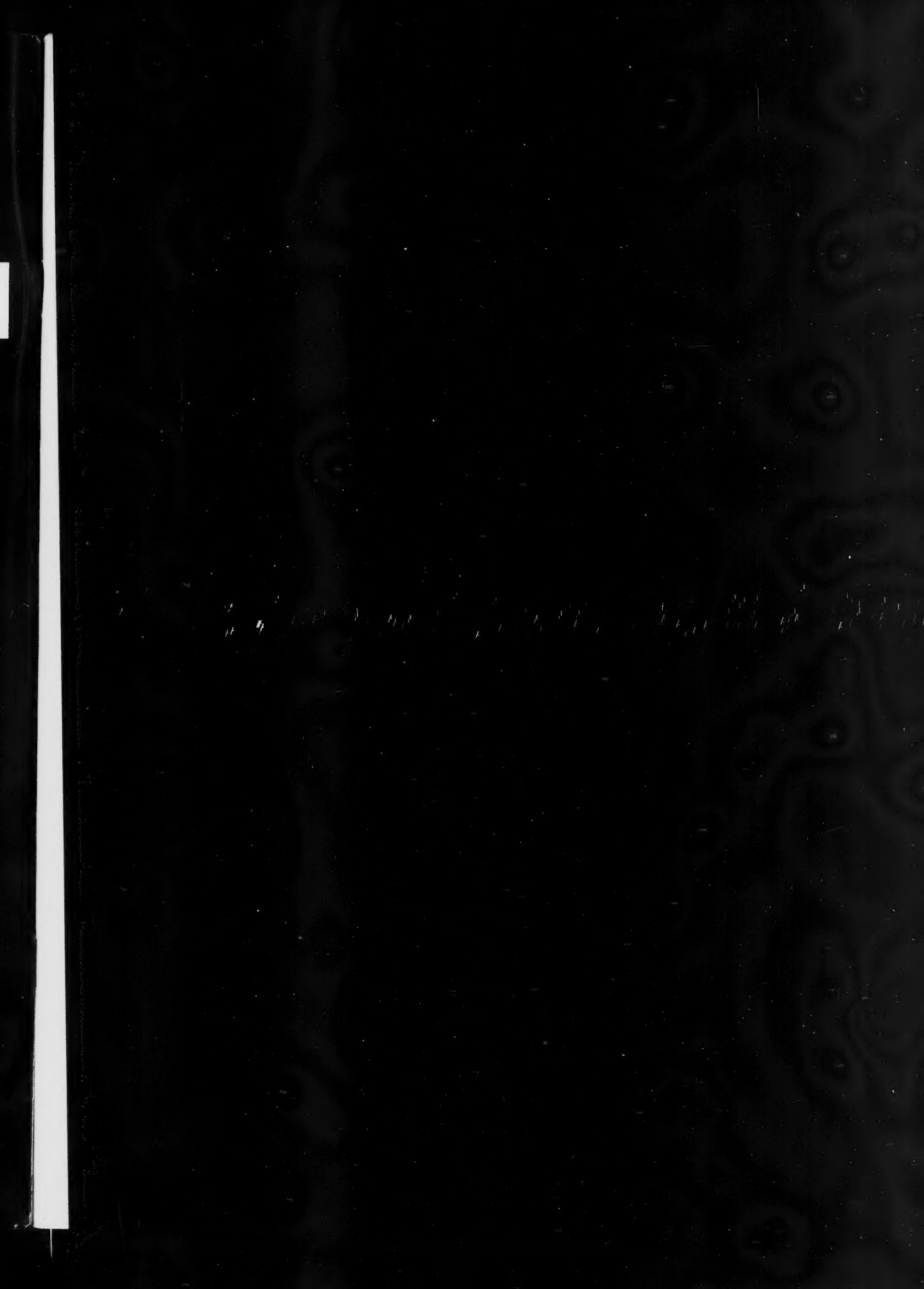

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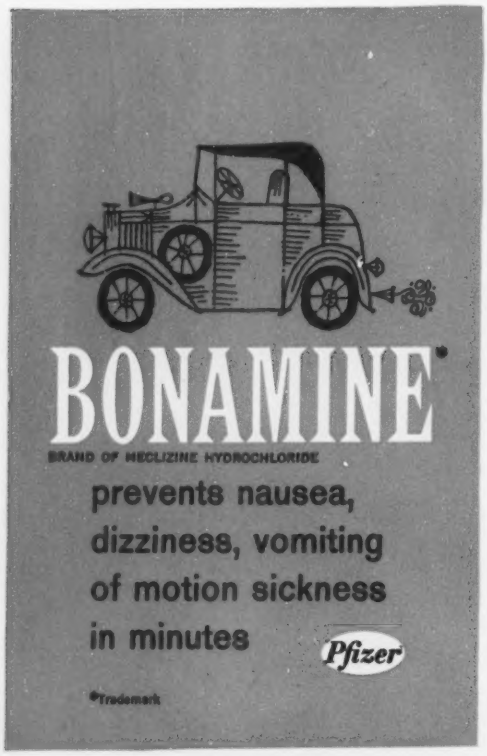


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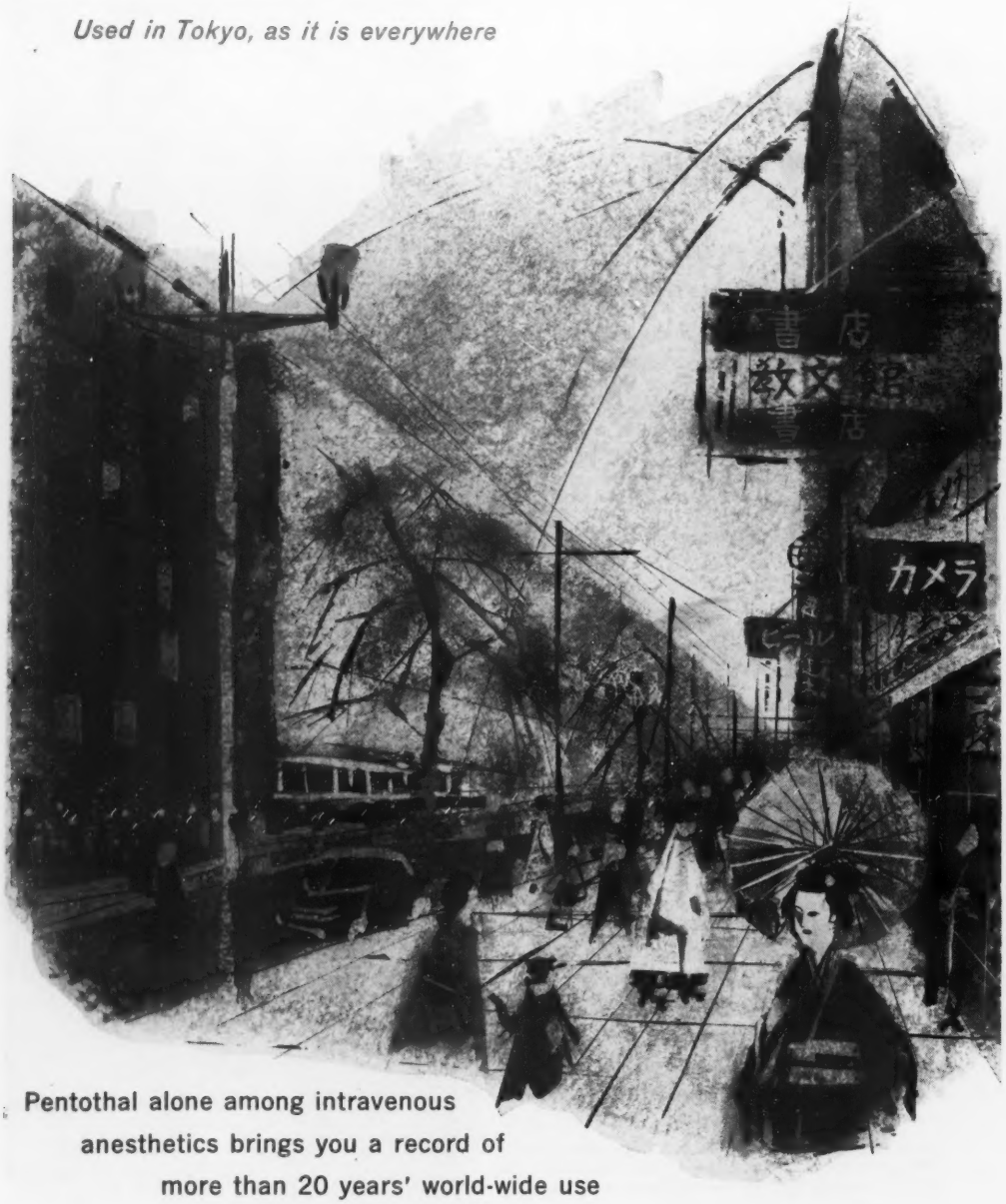


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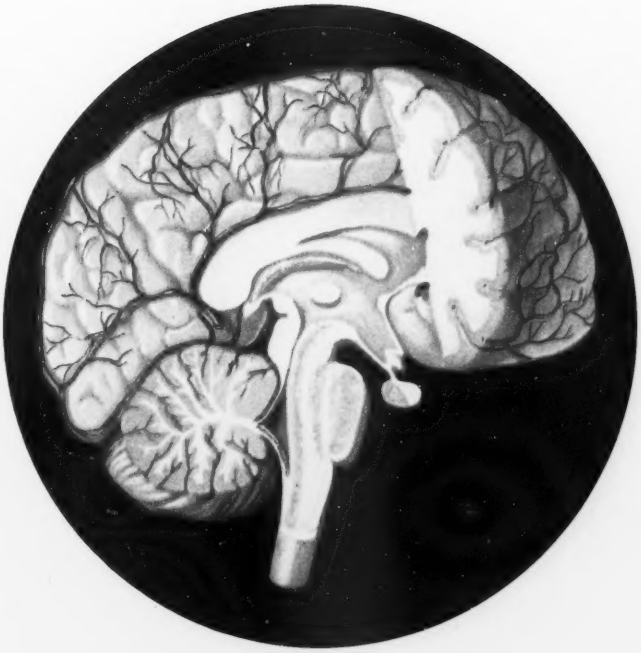

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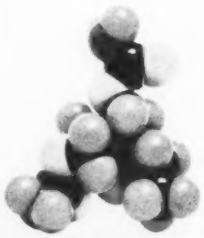

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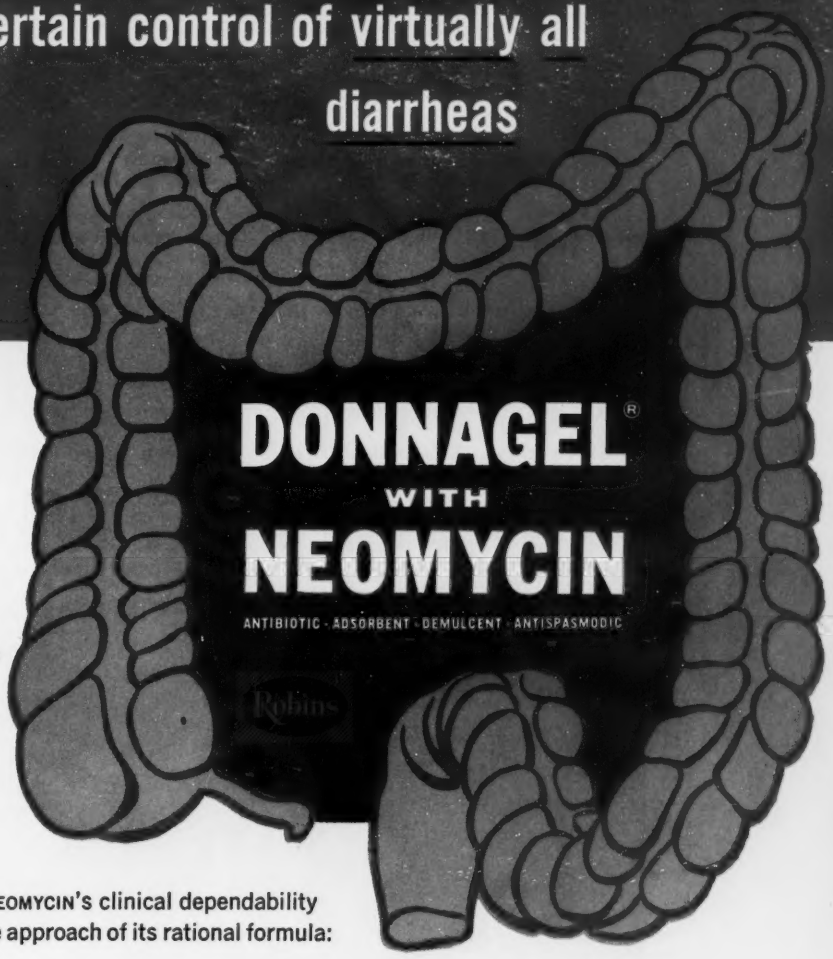


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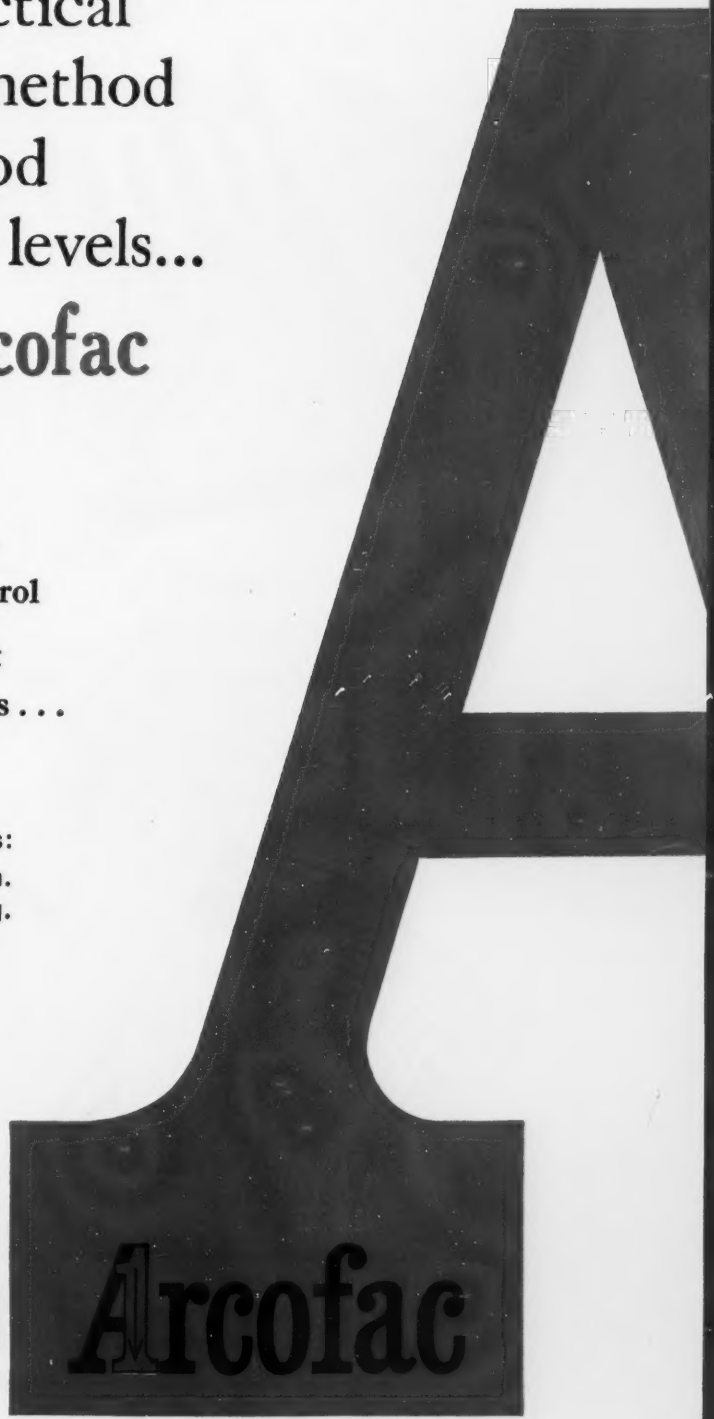


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**Volume LVIII** **AUGUST, 1957** **No. 8**

# Ureteral Injury

## *A Complication of Pelvic Surgery Which Can Be Baffling and Serious*

**D. CRAMER REED, M.D.,** ***Wichita, and*** **A. I. DODSON, M.D.,** ***Richmond, Virginia***

There is general agreement among surgeons and gynecologists that ureteral injuries constitute one of the most serious surgical accidents with which they contend. It behooves us therefore to periodically examine the various aspects of this problem, because, as stated by Barrett:[1] "Even the most expert and experienced surgeon may find himself one day contemplating an injured ureter, no matter how wary he may be." Because of the close relationship of the distal ureter to the important pelvic structures, 75 per cent of the injuries take place in the lower one-third. Therefore, this essay will be limited to a discussion of surgical injuries involving the distal ureter.

### History and Incidence

Injury to one or both ureters during operative procedures dates back to the initial days of pelvic surgery. Conger[2] reports that Simon in 1869 performed a cutaneous ureterostomy following ureteral injury during an ovarian operation. Twenty-six years later Tuffner reported 40 cases of ureterovaginal fistula following vaginal hysterectomy. Since the beginning of the 20th century numerous others, mostly urologists, have published papers dealing with the incidence and treatment of such injuries.

A review of the literature indicates that accidental ureteral injury occurring in the course of pelvic or radical exenterating procedures has a reported incidence of one to three per cent. That the actual incidence of such injuries may be considerably higher is unquestioned for several reasons by such authors as Barrett,[1] Bland,[3] Eddy,[4] Newell,[5] and Patton.[6]

**A five-year study of 3,414 surgical procedures is reviewed with reference to ureteral injury. The literature on the subject is briefly reviewed, and two case reports are presented.**

First, there appears to be a substantial number of silent unilateral ureteral injuries in which the patient suffers hydronephrotic atrophy without localizing symptoms. Another reason cited is the understandable reluctance of operating surgeons to publish reports of such complications, and since the urologist usually enters the case in the capacity of a consultant there is a disinclination to request permission to report another's complications.

A compilation of statistics from the Hospital Division of the Medical College of Virginia indicates that in the performance of 494 major gynecologic procedures on the ward service during 1950 and 1951, there were nine cases of ureteral injury, giving an incidence of 1.8 per cent. Analysis of these injuries indicates that in eight instances the ureter was divided, in two cases ligated, and in one kinked by a ligature.

Regarding the diagnosis of unsuspected ureteral injury, Hooper and Hill[7] performed an interesting

Dr. Reed formerly was an instructor in urology at the Medical College of Virginia, Richmond. Dr. Dodson is professor of urology at that medical school.

chromocystoscopic study on 100 patients undergoing major gynecologic surgical procedures on the ward service of the Hospital Division of the Medical College of Virginia. This consisted of performing a cystoscopic examination prior to and following surgery and observing the time of differential renal excretion for indigo carmine injected intravenously. While the procedure lacks practicability for routine employment, it was responsible for detecting three unsuspected instances of ureteral injury resulting in renal damage.

In 1953 Horrax and Conger[2] carried out pre- and postoperative intravenous urograms on 200 patients undergoing similar operations and found only one case of silent ureteral obstruction. On the basis of these studies, one might question the presumed high incidence of undiagnosed injuries. A more recent survey of statistics from the Hospital Division of the Medical College of Virginia reveals a total of eight injuries occurring on both the private and ward services between 1954 and 1955 in a total of 931 major gynecologic procedures, for an incidence of 0.85 per cent. An analysis of these injuries indicates five were unilateral and three bilateral; four were produced by division, three by ligation and one by kinking.

## Pathogenesis

Regarding the types of surgical procedures most frequently associated with ureteral injury, the following tabulation is a composite of the experiences of Moore,[8] Leventhal,[9] Faulk,[10] and Aschner:[11]

Radical hysterectomy
Total hysterectomy (abdominal)
Supracervical hysterectomy
Vaginal hysterectomy
Salpingo-oophorectomy for pelvic inflammatory disease
Anterior colporrhaphy
Radical operation for carcinoma of the rectum and rectosigmoid

The first four procedures account for the great majority of injuries. A study of the types of injury produced shows that some form of division accounts for most of those recognized at the time of operation, with ligation, crushing and stripping the ureter of its perureteral sheath and accompanying blood supply constituting the main causes of delayed injury. Statistically, unilateral ligation is the most frequently encountered type of surgical injury. Fortunately bilateral ligation is uncommon. Most direct injuries are said to occur in controlling hemorrhage, or incident to the removal of extensive malignant tumors, according to Barrett[1] and Newell.[5] In urologic surgery the ureter is most susceptible to injury during the resection of large vesical diverticuli. Of the 26 papers reviewed, only Patton[6] expressed the opinion that extensive stripping of the intact ureter is probably rarely complicated by ischemic necrosis; most essayists agree that such a procedure not infrequently results in postoperative ureteral fistula.

The immediate pathologic changes are fistula, extravasation of urine with accompanying cellulitis, or peritonitis. In the case of gynecologic surgery, the urine usually infiltrates the pelvic tissues and is eventually discharged through the abdominal wound, cervical stump, or vaginal cuff. Obviously when urine is excreted into the abdominal cavity a chemical peritonitis of some degree occurs. The magnitude of the reaction is rather dependent upon the degree of infection present, for the peritoneum is exceptionally tolerant of sterile urine. The time elapsing between the injury and fistula formation depends upon the nature of the injury, as will be subsequently discussed.

The contused or ligated ureter does not necessarily result in fistula or permanent renal damage. Spontaneous recovery occasionally occurs if the blood supply is adequate and, in the case of ligation, if the suture is absorbed and the ureteral lumen is re-established. In either case strictures are prone to develop and ultimate renal destruction results if they are not dilated. It is generally believed that when the ureter is completely occluded, immediate hydronephrosis and subsequent renal atrophy develop, frequently without symptoms. In the case of ureteral fistula formation there is usually incomplete drainage, but renal excretion continues, resulting in gradual ureterectasis and progressive, frequently symptomatic hydronephrosis. Renal destruction in such instances is greatly hastened when the hydronephrosis is complicated by infection.

## Prophylaxis

The best prophylaxis is to bear in mind the possibility of injuring the ureters whenever they lie near the field of operation. Also, most authorities suggest that following an extensive operation involving the true pelvis the ureters should be identified if possible prior to wound closure.

Sampson,[12] in 1902, was the first gynecologist to recommend preoperative catheterization of both ureters to prevent injury during hysterectomy. Since then the controversy regarding the propriety of such a prophylactic measure has continued unabated and today receives its main support from the urologist. However, even in the urologic ranks there are a few dissenters such as Riches,[13] who states: "The prophylactic introduction of ureteral catheters is a sad reflection on an operator's self confidence and betokens an inadequate knowledge of the anatomy of the pelvis and its pathological anatomy."

Faulk and Bunkin[10] cite certain objections to the preoperative insertion of ureteral catheters: (1) inability to palpate them; (2) impartation of a false sense of security; (3) alteration of normal ureteral position, thus making it more liable to injury; (4) possibility of initiating urinary tract infection leading to oliguria or reflex anuria. Leventhal,[9] and Wharton[14] are of the opinion that the use of ureteral catheters is obsolete.

However, with all due respect for the objections cited, there is an abundance of accumulated evidence presented by such authorities as Sisk,[15] Whitlock,[16] Landsteiner,[17] and Moore[8] indicating that the preliminary insertion of ureteral catheters is a wise precaution, not only in radical gynecologic surgery but also prior to such operations as extensive retroperitoneal node dissections and abdomino-perineal resections.

In a recent five-year period during which 3,414 major gynecologic procedures were performed at the Medical College of Virginia, no injuries occurred in patients with indwelling ureteral catheters. Thus while few will agree with Aschner that ureteral catheters should be passed in every case before pelvic surgery, the consensus is in favor of pre-operative ureteral catheterization in pelvic operations of anticipated difficulty.

It is surprising how few authors recommend preoperative intravenous urography, which in our opinion is particularly desirable if catheters are not introduced. Landsteiner[17] has listed the benefits of such a study: (1) affords an estimate of renal function and bilateral anatomy; (2) provides a warning of any involvement of the ureters in the pelvic disease; (3) provides means for discovering preexisting renal and ureteral abnormalities, and, in the event of postoperative urinary complications, prevents such abnormalities from being attributed to the operating surgeon. To these benefits we would add that information imparted by this or some other type of preoperative differential renal function test is imperative before consideration can be given to the feasibility of ligating an injured ureter, even under the most urgent circumstances.

## Symptoms and Diagnosis

Most authors emphasize that ureteral injury, unfortunately, is usually unrecognized at the time of the original operation. Postoperative urinary extravasation even into the peritoneal cavity may not be recognized because of the general discomfort and abdominal distention incident to an extensive procedure. However, when pain, distention, toxic symptoms, hematuria, anuria or oliguria, unusual fever, or costovertebral tenderness develop in the immediate postoperative period, ureteral injury must be considered. Pain and tenderness in the kidney area in such cases are rarely severe and often unnoted, as exemplified in the following case report of L. J.

Renal symptoms are more apt to occur when the ureter has been ligated in the presence of infected urine. Urinary drainage from the abdominal wound or vagina occurs in approximately 50 per cent of reported injuries and is highly indicative of ureteral fistula. It is noteworthy that Adams,[18] in his series of 26 injury cases, established that the majority developed fistula formation from the second to fourth and 12th to 14th postoperative days, but that some fistulae did not develop until the third or fourth week. It would seem logical to assume that the appearance of a fistula within a few hours following surgery is due to incision or division of the ureter. Conversely fistula formation resulting from crushing, ligation, or stripping the ureter is most often delayed days or weeks.

While cystoscopy is the most important diagnostic procedure and should be performed immediately in every suspected case of injury, the additional procedures employed depend primarily on the type of injury suspected. For example, to distinguish a ureterovaginal from a vesicovaginal fistula, cystoscopy may be employed or the bladder filled with methylene blue and note taken concerning whether clear urine continues to leak from the vagina. In other instances excretory or retrograde pyelography may be necessary to identify the exact locus of injury, status of renal function, and extent of hydronephrosis. While these clinical aids usually suffice for a diagnosis, there are a certain number of cases of complex involvement in which it is impossible to make a preoperative diagnosis.

## Management

Quite obviously the primary aim of ureteral injury treatment is twofold: (1) renal preservation and (2) ultimate restoration of urinary tract continuity to as near a normal state as possible. That neither of these goals is achieved in all cases reflects the fact we must continue to enhance our knowledge of ureteral pathologic physiology and surgical acumen if we hope to improve our operative statistics.

There appears to be universal agreement concerning certain fundamental principles of treatment of such injuries, namely: (1) adequate extra-peritoneal drainage in the prevention of extravasation; (2) early recognition and repair of injury; (3) avoidance of deliberate ureteral ligation for the purpose of producing hydronephrotic atrophy; (4) diversion of the urinary stream above the point of injury to protect the kidney and prevent extravasation at the injury site; and (5) employment of polyethylene or plastic tubing for splinting purposes since they are

considered superior to all other materials. However, D. M. Davis[25] has recently reported two serious antigenic reactions from such synthetic splints, resulting in ureteral granulomas. While we have not encountered such complications, the warning cannot be ignored.

Because the circumstances of the injury and the causative agent will vary, the management of each case presents an individual problem. Thus, only the highlights of treatment under certain standardized situations can be touched upon.

Injuries recognized *during* the operation can be discussed under two general headings: (1) ureteral ligation or crushing and (2) partial or complete ureteral division. There appears to be no controversy about the first type of injury because removal of the ligature from about the ureter is usually sufficient, although occasionally fistula results when the ligature has remained only a short time. Therefore, it is recommended that a ureteral splinting catheter of adequate calibre be introduced postoperatively and allowed to remain two to three weeks, as in the case of crushing injuries of short duration.

When the ureter has been severely traumatized with prolonged clamping, it is safer to resect the devitalized area and anastomose the ureter or implant the proximal end into the bladder. When the ureter is only partially severed, it should be immediately repaired with interrupted fine chromic suture material, care being taken not to penetrate the mucosa. Riches and Dodson[19] recommend in cases of end to end anastomosis that a small opening in the ureter above the anastomosis be made through which a catheter is passed into the renal pelvis, thus completely diverting the urinary stream.

The procedure of choice when the ureter is severed below the pelvic brim and not more than 5 cm. from the bladder is ureteroneocystostomy with placement of the ureteral orifice as near the trigone as possible. When transection occurs too high for reimplantation, end to end uretero-ureteral anastomosis is indicated. There is no unanimity concerning the best treatment for cases where a segment of the ureter has been excised. Some recommend cutaneous ureterostomy, others ureterosigmoid anastomosis, each having well appreciated disadvantages which, in our opinion, make the methods undesirable. Trans-uretero-ureteral anastomosis is technically a difficult procedure and, in spite of Moore's success, always carries the risk of failure with irreversible damage to the originally uninvolved ureter.

In the last two years considerable attention has been focused on ureteroileocystoplasty in cases of permanently damaged ureters; such a procedure is mechanically and technically feasible.[26] Ureteral ligation has generally been condemned; however, such a temporary precedure might well be indicated in a poor risk patient where the urine is known to be sterile and function of the opposite kidney known to be adequate. This statement is made in view of Moore's report of a case in which the ureter was occluded for three months. After corrective surgery the kidney resumed its normal function. Regardless of the type of treatment employed, it is paramount that extraperitoneal drainage be established to the injury site.

Injuries recognized *after completion* of the operative procedure constitute the greatest number with which we have to contend. It is also a group concerning which there is considerable variation of opinion. While many modern authors (Whitlock, Patton, Aschner, Moore, and Feiner[20]) consider immediate bilateral deligation a hazardous and difficult procedure, Conger, Rolnick,[21] Herman,[22] and a few others recommend that the abdominal incision be reopened within 24 to 48 hours, providing the patient's condition permits and it is impossible to pass a catheter beyond the obstructions. The majority of urologists would favor temporary nephrostomy as being the safer procedure.

When only one ureter is occluded, if the opposite kidney is functioning normally and there is no evidence of renal infection, a conservative nonoperative course is advised by a few; most, however, recom-

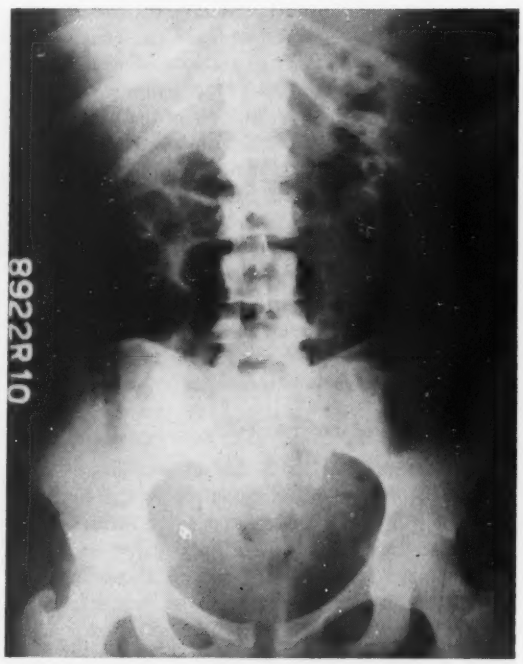


Figure 1. Left hydronephrosis with calyectasis and non-functioning right kidney.

mend neocystostomy as soon as the patient's condition permits and before dense adhesions have had time to form.

When unilateral uretero-cutaneous or ureterovaginal fistula occurs, operation may be deferred until the patient has recovered from the primary operative procedure—provided there is adequate uretero-fistula drainage, or nephrostomy or ureterostomy has been performed as a preliminary step. If the involved side has good function, etc., the drainage channel should ultimately be re-established either by end to end anastomosis or ureterovesical implantation, the latter being preferable if the proximal ureteral segment will reach directly or with the aid of a bladder flap as described by Ockerblad.[23, 24] If there is evidence of renal damage or infection on the involved side, nephrectomy will give the best results unless the opposite kidney is also deficient.

## Case Reports

Two typical case histories will be presented to illustrate certain of the problems encountered in the diagnosis and care of patients with ureteral injuries. The first case report is illustrative of a postpartum hysterectomy complication; the second depicts the potential hazard of routine hysterectomy and demonstrates the value of perseverance in caring for such injuries.

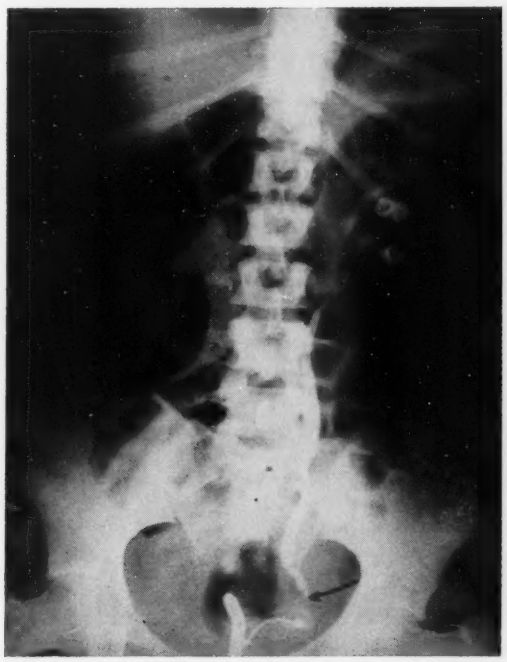

Figure 2. Acorn-tip catheter injection demonstrating kinking and stenosis of the distal left ureter.

Figure 3. Acorn-tip catheter injection of right ureter indicating complete obstruction. Left hydronephrosis is demonstrated.

L. J., a 29-year-old Gravida VII, Para VI Negro female, was admitted to the Obstetrical Division, Medical College of Virginia, in April, 1955, because of premature rupture of membranes. Following delivery uterine hemorrhage occurred and was uncontrolled by intra-uterine packing or curettement, necessitating an easily performed total abdominal hysterectomy 10 hours postpartum.

Gross painless hematuria developed immediately after surgery and was attributed to bladder trauma incident to the surgery. A decreased urinary output was believed to be secondary to impaired renal blood flow occurring prior to and again during surgery as a result of excessive blood loss. Thirty-six hours after surgery the gross hematuria cleared, and the patient's urinary output improved as she became afebrile.

Because of persistent microscopic hematuria, an intravenous pyelogram was performed six days following hysterectomy (Figure 1), revealing left hydronephrosis and a non-functioning right kidney. The patient continued to demonstrate no localizing symptoms. Retrograde pyelography was immediately performed, demonstrating kinking and marked stenosis of the distal four centimeters of the left ureter (Figure 2). At this time a small calibre catheter was fortuitously inserted past the obstruction and

Figure 4. Intravenous pyelogram ten days postoperatively demonstrating return of right renal function. Note normal configuration of left renal pelvis.

into the left renal pelvis. Numerous attempts to insert various types of catheters beyond a point 3 cm. proximal to the right ureteral meatus were unsuccessful. Foley cone tip catheter injection of the right ureter indicated a complete obstruction involving the terminal portion of the ureter (Figure 3).

During the ensuing four days it was possible to replace the No. 4 French left ureteral catheter with a No. 6. Thus adequate drainage was assured for the left kidney. The patient remained afebrile and without right renal symptoms.

Eleven days postoperatively an extra peritoneal right ureteroneocystostomy was performed with moderate difficulty due to retroperitoneal edema in the region of the bladder and at the level of the broad ligament. It was found that the ureter had been included in a transfixed ligature also placed about the right uterine artery. Because of the marked hydroureter formation proximal to the point of ligation, a No. 12 French levine tube was employed as a splint for the re-implanted ureter previously severed at the proximal point of obstruction some 3 cm. above the bladder (Figure 4).

The right ureteral splint tube was left in place 16 days; the left ureteral catheter remained in place for 10 days. Following their removal the patient continued to make an uneventful recovery and was dismissed from the hospital 20 days after the urologic surgery.

An intravenous pyelogram six weeks later (Figure 5) indicated satisfactory bilateral function with evidence of residual right pyelonephritis and an essentially normal-appearing left kidney. Left ureteral calibration and dilatation were subsequently performed every six weeks for the following six months.

C. S., a 41-year-old Negro, was admitted to the Surgical Service, Medical College of Virginia, in January, 1955, with a diagnosis of large uterine leiomyomata, chronic cervicitis and salpingitis, and a left ovarian cyst.

Three days later a total abdominal hysterectomy and left salpingo-oophorectomy were performed. During the operation in an effort to control vigorous bleeding from the left uterine artery, the adjacent ureter was clamped and severed. A primary end to end uretero-ureteral anastomosis was performed employing a number 7 ureteral catheter as a splint (Figure 6). Extra peritoneal drainage was established by placing a Penrose drain in the immediate area of the repair and allowing it to emerge through the vaginal cuff. The distal end of the splint tube was subsequently removed from the bladder by cystos-

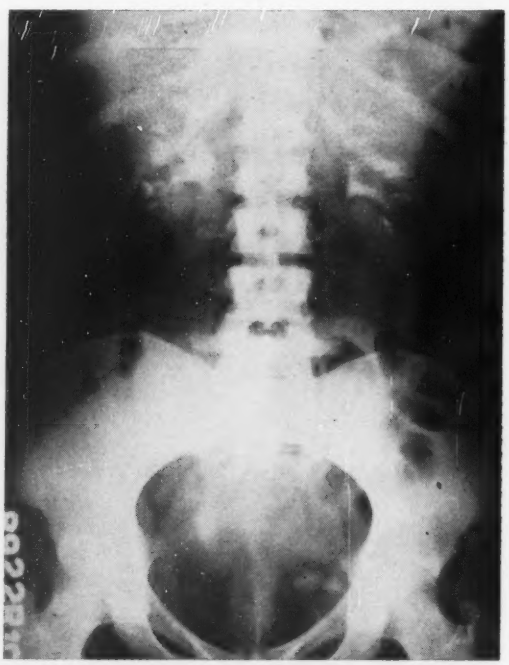

Figure 5. Intravenous pyelogram six weeks postoperatively demonstrating minimal calyceal distortion.

copy, and it was secured to a Foley catheter placed in the bladder.

On the fifth postoperative day the patient developed acute bronchial asthma and signs and symptoms of intestinal obstruction. In the performance of x-ray studies to establish the diagnosis, the Foley catheter became deflated and was ultimately removed with the attached ureteral splinting catheter. Immediate cystoscopic efforts to catheterize the left ureter were unsuccessful. Because of the patient's precarious condition, no further operative procedures were attempted until the asthmatic crisis was controlled by corticotrophic hormones and the severe ileus by gastric suction.

The patient immediately developed a ureterovaginal fistula following removal of the splinting catheter, associated with hydronephrosis, chills, and fever. By the seventh postoperative day her general condition was sufficiently improved to permit a left nephrostomy and successful antegrade ureteral intubation with the distal tip of the catheter placed within the bladder. The splinting catheter was removed through the nephrostomy wound in 12 days. Immediately the patient had chills and fever for six days, presumably due to a proteus vulgaris left pyelonephritis which was ultimately controlled by

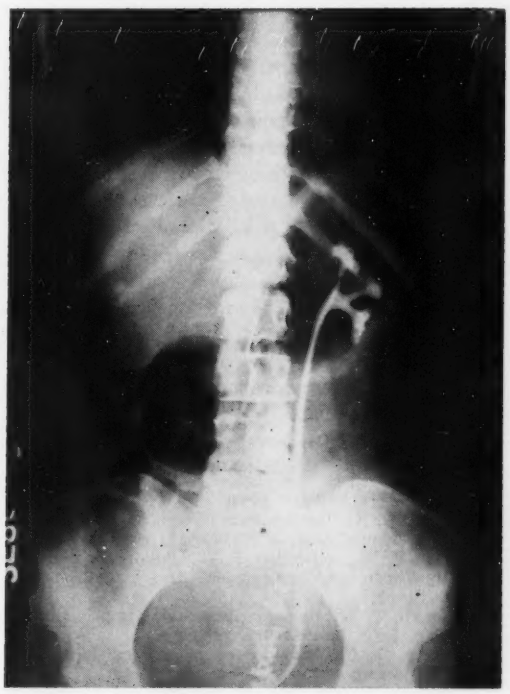

Figure 6. Postoperative film demonstrating excellent positioning of left ureteral splinting catheter.

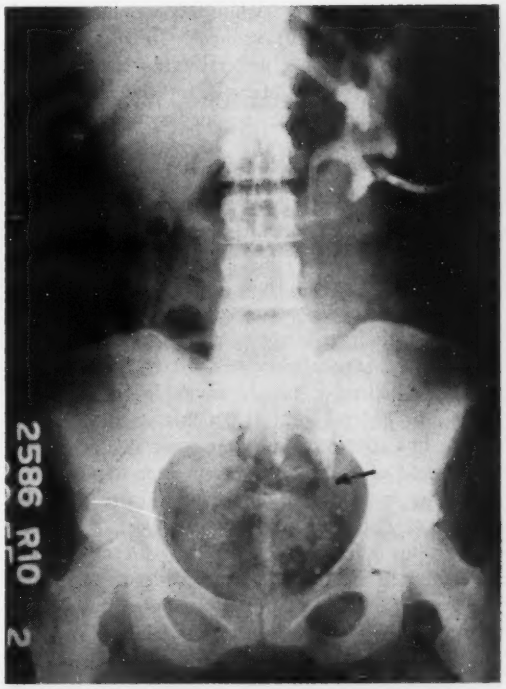


Figure 7. Nephrostomy tube antegrade left pyelogram demonstrating ureteral dilatation proximal to the anastomosis.

Chloromycetin combined with Gantrisin. There was no evidence of fistulous drainage at this time; however, the ureter was not visualized in its distal one-third and appeared dilated proximal to the anastomotic site (Figure 7).

Following the performance of an antegrade pyelogram on the patient's 22nd postoperative day, she was dismissed afebrile, ambulatory, with instructions to maintain the nephrostomy drainage because of extravasation at the anastomotic site and recurrence of the vaginal urinary fistula upon clamping of the nephrostomy tube (Figure 8).

The patient was carefully followed as an outpatient in the Urology Clinic, and 14 days following dismissal the fistulous drainage spontaneously ceased. Twenty days later an antegrated pyelogram revealed satisfactory renal drainage and no extravasation; thus the nephrostomy tube was removed.

The patient remained asymptomatic; however, in April, 1955, left ureteral dilatation was performed with ease and no stricture was encountered. Two weeks later an intravenous pyelogram revealed satisfactory renal function but left calyceal distortion and evidence of left renal damage which accounted

for her pyuria of 3 to 5 white blood count per high power field (Figure 9).

As in the first case, ureteral calibration was carried out at six-week intervals for the ensuing six months, and the patient remained symptom-free.

## Summary and Conclusions

1. In a five-year study of 3,414 major gynecologic surgical procedures at the Hospital Division of the Medical College of Virginia, there were 24 ureteral injuries giving an incidence of 0.70 per cent.

2. An attempt has been made to review the pathogenesis, pathology, diagnosis, and general management of the surgically injured ureter.

3. We believe it highly advisable for all gynecologic or general surgical patients upon whom extensive operative procedures are contemplated to have the benefit of a urologic survey prior to surgery.

4. The introduction of inlying ureteral catheters immediately before extensive surgical procedures will, in our opinion, safeguard the patient; it should also enhance the operator's medico-legal position in the event that ureteral injury occurs, a situation unlikely to arise if this precaution is taken.

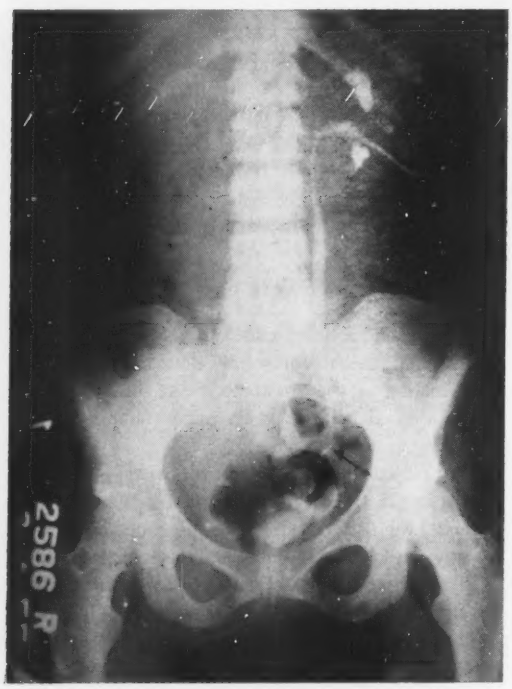


Figure 8. Antegrade pyelogram performed on 22nd postoperative day. Note extravasation of contrast media at site of anastomosis. Ureteral dilatation is less than in Figure 7.

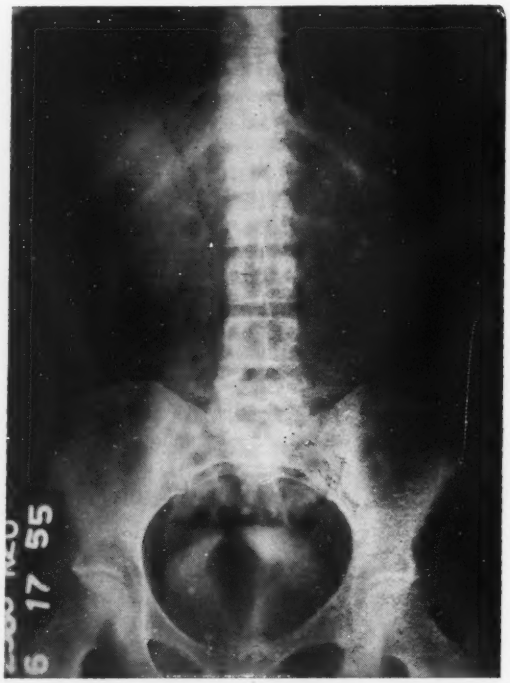


Figure 9. Intravenous pyelogram six months postoperatively revealing satisfactory left renal function.

5. Further experimental studies are indicated to ascertain how long the kidney can be completely obstructed and still be expected to recover with reestablishment of the ureteral channel. It is conceivable that the deliberate temporary ligation of the proximal end of a sectioned ureter under certain circumstances would be practical and safe.

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# Serum Transaminase

## *Clinical Experience with 211 Patients*

**LEITHA D. BUNCH, M.A., W. H. ARCHER, B.A., *and* G. L. NORRIS, M.D., *Winfield***

The determination of serum transaminase values is proving to be a valuable adjunct in the diagnosis of certain diseases, especially of the heart and liver. That serum glutamic oxalacetic transaminase (SGO-T) is elevated following acute myocardial infarction is well established. This enzyme is also increased in hepatic necrosis. Serum glutamic pyruvic transaminase (SGP-T) is not appreciably elevated following acute cardiac necrosis but is more sensitive than SGO-T in diagnosing acute hepatocellular damage. In this paper we are reporting some results of transaminase studies in patients in whom the test was of definite value in the diagnosis and management of the diseased state.

### Methods and Individuals Studied

SGO-T was measured by a modification of the spectrophotometric method of Karman, Wroblewski, and LaDue.[9] The modifications were essentially those of Steinberg and Ostrow[3] and Steinberg, Baldwin, and Ostrow.[10] The SGP-T method used was basically that of Wroblewski and LaDue[7] with the same modifications as used in SGO-T measurements. The SGO-T activity of a given serum was found to be stable, especially if the serum was kept frozen. Even at room temperature, the activity does not change appreciably for several days.

SGP-T activity is not so stable as SGO-T. The loss of activity is erratic from sample to sample, even in those samples kept frozen. To get reliable SGP-T values, we have found it advisable to analyze the serum within a few hours after the blood is drawn. If serum stands on the clot for more than a few hours, it acquires the tendency of almost instantaneously oxidizing diphosphopyridine nucleotide (DPNH). To check uniformity in reactions, we have run a "known" serum sample with each battery of unknowns, preferably using a sample with activity at the upper limit of normal. The units used in this paper are those of Karmen et al.[9]

In the past nine months, 386 SGO-T and 215 SGP-T determinations have been made on 211 patients in our laboratory. The individuals were private patients of the Snyder Clinic, Winfield, or patients at the Winfield State Training School, an institution for the mentally retarded. To establish normal values, 104 SGO-T and 47 SGP-T determinations were done on 77 healthy controls. We were measuring SGO-T activity several months before we were measuring SGP-T activity. To allow fuller use of the material presented here, parallel data on the two enzymes would have been ideal.

**Determination of SGO-T and SGP-T values is of help in both diagnosis and therapy of patients with acute myocardial infarctions and diseases of the hepatobiliary system. Preliminary results indicate that more data will assist in differentiating between hepatocellular and obstructive jaundice.**

To establish diagnosis in each case, the usual diagnostic techniques, including electrocardiogram and x-ray studies as needed, were carried out. In patients with suspected liver disease, other biochemical tests done were serum cholinesterase (ChE), cephalin flocculation, thymol turbidity, alkaline phosphatase, and total and esterified cholesterol. Normal values for these characteristics had previously been established in our laboratory. Blood samples were drawn from patients in the fasting state in those in whom we were following the battery of liver function tests. In initial samples drawn from patients with suspected myocardial infarction, blood was drawn without regard for meals. In determining normal transaminase activities, serum samples were not necessarily from individuals in the basal state.

### Results

In Table 1 are shown some results on patients with

From The H. L. Snyder Memorial Research Foundation, Winfield. The authors wish to thank the staffs of the Snyder Clinic and the Winfield State Training School Hospital for the use of their clinical material. Especially appreciated is the cooperation of Bryce Hinkson, M.D., resident in internal medicine, Winfield State Training School.

Reagents for SGO-T and SGP-T determinations were obtained from the California Foundation for Biochemical Research, Los Angeles, except lactic dehydrogenase. That was obtained from Delta Chemical Works, New York, or Sigma Chemical Company, St. Louis.

TABLE 1
ACUTE MYOCARDIAL INFARCTIONS

| *Patient* | *Remarks* | *Date* | *SGO-T* | *SGP-T* |
|---|---|---|---|---|
| WP | Acute myocardial infarction—blood drawn | | | |
| | 2 hrs. after onset of pain | 5-14-56 | 19.0 | |
| | 19 hrs. after onset of pain | 5-15-56 | 108.0 | |
| | | 5-16-56 | 75.0 | |
| | | 5-18-56 | 25.0 | |
| | | 5-24-56 | 15.0 | |
| | | 12-11-56 | 15.0 | |
| CC | Hospital admission | 7-28-56 | 10.0 | 7.0 |
| | Acute myocardial infarction 8-1-56 | 8-1-56 | 482.0 | 70.0 |
| | | 8-2-56 | 182.0 | 55.0 |
| | | 8-7-56 | 20.0 | 72.0 |
| | | 8-15-56 | 76.0 | 164.0 |
| | Deceased 8-16-56. Severe chronic passive congestion of liver, gastric hemorrhage found at autopsy. | | | |
| AS | Acute myocardial infarction 1-23-57 | | | |
| | | 1-24-57 | 225.0 | 30.0 |
| | | 1-25-57 | 140.0 | 34.0 |
| | Improving clinically | 1-26-57 | 89.0 | 49.0 |
| FA | Acute myocardial infarction 12-3-56 | 12-3-56 | 52.0 | 14.0 |
| | | 12-4-56 | 38.5 | 13.0 |
| | Pulmonary emboli with infarctions 12-17-56 | 12-17-56 | 30.0 | 27.5 |
| | | 12-29-56 | 24.5 | 39.5 |
| CG | Acute myocardial infarction 4-18-56 | | | |
| | On chlorpromazine from 4-19-56 | 4-19-56 | 60.0 | |
| | through 5-9-56 | 4-20-56 | 42.0 | |
| | | 4-21-56 | 38.0 | |
| | | 4-24-56 | 40.0 | |
| | | 5-1-56 | 35.0 | |
| | | 5-8-56 | 77.0 | |
| | | 5-9-56 | 89.0 | |
| SJ | Hospital admission | 11-19-56 | 20.0 | 15.0 |
| | Arteriosclerosis with anginal syndrome | 11-21-56 | 11.0 | 12.0 |
| | Acute anterior myocardial infarction | 12-1-56 | 77.0 | 14.0 |
| VM | Acute myocardial infarction 9-10-56 | | | |
| | Deceased later this date | 9-11-56 | 74.0 | 19.0 |
| BM | Acute posterior myocardial infarction, 7-11-56, 2:30 PM | | | |
| | 17 hrs. after onset of pain | 7-12-56 | 94.0 | 20.0 |
| | | 7-17-56 | 10.0 | 14.0 |
| HM | Uremia, salt losing nephritis | 5-22-56 | 10.9 | |
| | Acute myocardial infarction 6-3-56 | | | |
| | | 6-4-56 | 460.0 | |
| | Deceased 6-5-56 | | | |
| DL | Acute myocardial infarction 3-2-56 | | | |
| | | 3-7-56 | 50.8 | |
| | | 3-14-56 | 31.3 | |
| | Deceased 3-15-56 | | | |
| Healthy Controls | No. | | 77 | 37 |
| | Range | | 8.5-29.2 | 5.5-22.5 |
| | Mean | | 14.6 | 12.1 |

acute myocardial infarctions, along with mean normal values for SGO-T and SGP-T. The time of drawing blood for transaminase assay, in relation to time of attack, is important. In patient W.P., the first blood sample was drawn within a few hours after the suspected infarction. The transaminase value was normal, but in a sample drawn 19 hours after the onset of pain it was elevated to 108 SGO-T units. The value had returned to normal in four days.

The highest SGO-T observed in our series was 482 units in patient C.C. In the same serum sample, SGP-T activity was elevated to 70 units. The SGO-T fell rapidly to a value of 20 units six days after the infarction, but the SGP-T value was increased over the preceding value. The sample drawn the day before death showed SGP-T value of 164 units and SGO-T of 76 units. This elevation of SGP-T in excess to SGO-T was suggestive of liver disease. At autopsy it was found that there was severe chronic passive congestion of the liver and gastric hemorrhage.

In patient A.S., the first SGO-T determination (225 units) was helpful in establishing the diagnosis since the electrocardiogram showed complete A.V. block with idioventricular rhythm. Three days after the attack the SGO-T value had dropped to 89 units. The patient was improving clinically, with no complications. The upward trend of SGP-T cannot be explained, nor can the outcome of the illness be given since it is only four days since the infarction.

In patient F.A., the course of recovery from the myocardial infarction was complicated by pulmonary emboli with infarctions two weeks after the heart attack. The slight elevation of SGP-T found in the last sample reported here is probably a reflection of the liver damage resulting from the circumstances of the illness.

The pattern of SGO-T is different in patient C.G. than in any other patient shown in Table 1. The value fell rather slowly from 60 units on the day after the infarction to 35 units in 12 days, and it rose to 89 units in the next eight days. Repeated electrocardiograms and other diagnostic procedures did not show any evidence of a second infarction. The patient had been given chlorpromazine on admission to the hospital and was continued on this medication throughout the period of our observations. It is probable that this secondary rise in SGO-T was due to early drug toxicity, but we cannot be certain since studies could not be made after the drug was discontinued. It is unfortunate that SGP-T determinations were not done on this patient for they should have helped identify the source of the increased SGO-T.

Laboratory data from other patients shown in Table 1 are meager, but sufficient notes and dates are included to make the results self-explanatory.

In spite of the fact that SGP-T data was not taken on many samples, it is apparent in Table 1 that SGO-T is more sensitive to myocardial damage than SGP-T. After a rise in SGO-T activity following a heart attack, the enzyme level rapidly falls and reaches normal in two to seven days. The finding of normal SGO-T values in some patients has been helpful in ruling out acute myocardial infarctions. The time at which the blood sample is drawn, in relation to the infarction, is important. The abnormal level of SGO-T is not reached until about six hours after the attack and may not persist more than 24 to 72 hours after the infarction.

In Table 2 are shown the results of SGO-T and SGP-T from 10 patients with infectious hepatitis, along with results of other liver function tests. Normal values for all characteristics are shown. Of the 10, six were residents of the Winfield State Training School and three were employees of the same institution.

Both SGO-T and SGP-T values are many times greater than normal at the height of the illness. In all patients in whom both SGO-T and SGP-T studies were made, SGP-T is the higher of the two, although they rise and fall together. SGO-T values reach much higher levels in hepatitis than in myocardial infarctions, as can be seen by comparing data in Table 1 and Table 2. There is no consistent relationship between the transaminase values and any other liver function test. The magnitude of change in SGP-T values is much greater than in any of the more common tests. It is especially helpful to have a more sensitive test for such patients as C.B., who at no time had a serum bilirubin above normal. It is noteworthy that her highest bilirubin, 0.8 mg/100 ml., was found in the serum with the highest SGP-T value, 515 units. On admission to the hospital, this patient had anemia (Hb 7.3 gm/100 ml.), which responded promptly to iron therapy. Within any one case there is a reciprocal relationship between serum cholinesterase and SGO-T or SGP-T until the patient approaches recovery.

In Table 3 are given some results of serum transaminase and other liver function tests from a group of patients with diseases of the hepatobiliary system other than infectious hepatitis.

Patient S.C. had infectious mononucleosis with liver involvement. At the time he came under observation SGO-T activity was 173 units. Serum bilirubin, alkaline phosphatase, and thymol turbidity were each elevated and cephalin flocculation was 4 plus. With treatment, the clinical improvement of the patient was as rapid as the fall in SGO-T would indicate.

There are three patients in the group with chlorpromazine jaundice. Blood samples were drawn soon

TABLE 2
INFECTIOUS HEPATITIS

| *Patient* | *Date* | *SGP-T* | *SGO-T* | *Serum ChE* | *Bilirubin* | *Ceph. Flocc.* | *Thymol Turb.* | *Alk. Phosphatase* | *% Chol. esters* |
|---|---|---|---|---|---|---|---|---|---|
| | | UNITS | UNITS | UNITS | MG/100 ML | | UNITS | UNITS | |
| LJ | 7-6-56 | 1080 | 935 | 1.49 | 7.4 | 4+ | 2.7 | 10.6 | 51 |
| | 7-11-56 | 633 | 691 | 1.52 | 4.0 | 3+ | 2.4 | 10.6 | 61 |
| | 7-17-56 | 454 | 111 | 1.62 | 2.5 | 3+ | 2.2 | 6.7 | 73 |
| | 7-20-56 | 367 | 122 | 2.06 | 2.9 | 2+ | 2.4 | 6.7 | 65 |
| | 7-25-56 | 171 | 103 | 1.62 | 0.7 | 4+ | 1.7 | 5.7 | 55 |
| | 8-1-56 | 147 | 191 | 1.89 | 0.4 | 4+ | 0.8 | 6.0 | – |
| | 8-3-56 | 95 | 72 | — | — | – | – | – | – |
| | 8-15-56 | 47 | 25 | 2.05 | 0.1 | 3+ | 1.0 | 5.3 | – |
| | 8-22-56 | 29 | 38 | 1.98 | 0.1 | 2+ | 0.8 | 4.3 | – |
| | 8-29-56 | 18 | 24 | 2.15 | 0.2 | 0 | 0.6 | 4.0 | – |
| | 9-12-56 | 12 | 24 | 1.82 | 0.1 | 3+ | 0.5 | 3.7 | – |
| | 11-27-56 | 10 | — | 1.96 | 0.2 | 0 | 0.4 | 4.0 | 83 |
| LR | 8-17-56 | 1350 | 296 | 1.16 | 3.8 | 4+ | 1.3 | 21.4 | 48 |
| | 8-29-56 | 590 | 176 | 1.50 | 0.9 | 4+ | 0.8 | 13.2 | – |
| | 9-5-56 | 195 | 79 | 1.74 | 1.2 | 3+ | 0.6 | – | – |
| | 9-10-56 | 99 | 50 | 1.81 | 0.8 | 2+ | 0.4 | 13.8 | – |
| | 9-19-56 | 36 | 23 | 1.48 | 0.7 | 2+ | 0.7 | 12.2 | – |
| | 10-9-56 | 19 | 18 | 1.66 | 0.6 | 2+ | 0.3 | 7.4 | – |
| | 10-22-56 | 15 | 19 | 1.59 | 0.3 | 2+ | 0.3 | 6.9 | 72 |
| SB | 9-11-56 | 358 | 253 | 2.42 | 9.6 | 4+ | 2.7 | 20.1 | 56 |
| | 9-19-56 | 272 | 118 | 2.27 | 2.7 | 4+ | 3.2 | 14.2 | 73 |
| | 10-18-56 | 34 | 35 | 2.62 | 1.0 | 3+ | 1.0 | 6.4 | – |
| | 10-31-56 | 20 | 24 | 3.00 | 0.4 | 0 | 0.6 | 7.0 | – |
| | 1-9-57 | 7 | 14 | 3.19 | 0.4 | 1+ | 0.3 | 5.3 | 80 |
| MH | 8-4-56 | 303 | 102 | — | 17.4 | – | – | – | – |
| | 8-8-56 | 563 | 200 | 1.16 | 16.6 | 4+ | 1.6 | 16.3 | 14 |
| | 8-15-56 | 290 | 137 | 1.13 | 7.6 | 4+ | 1.6 | 17.1 | – |
| | 8-20-56 | 503 | 80 | 1.00 | 6.5 | 4+ | 1.7 | 19.1 | 21 |
| | 8-29-56 | 138 | 110 | 0.76 | 3.8 | 4+ | 1.8 | 18.6 | 68 |
| | 9-5-56 | 76 | 99 | 0.66 | 4.5 | 4+ | 1.6 | – | – |
| | 9-10-56 | 67 | 72 | 0.94 | 3.5 | 4+ | 1.3 | 14.7 | – |

TABLE 2 (Cont.)
INFECTIOUS HEPATITIS

| *Patient* | *Date* | *SGP-T* | *SGO-T* | *Serum ChE* | *Bilirubin* | *Ceph. Flocc.* | *Thymol Turb.* | *Alk. Phosphatase* | *% Chol. esters* |
|---|---|---|---|---|---|---|---|---|---|
| | | UNITS | UNITS | UNITS | MG/100 ML | | UNITS | UNITS | |
| | 9-19-56 | 42 | 61 | 0.98 | 2.5 | 3+ | 2.4 | 14.6 | – |
| | 9-28-56 | 44 | 58 | 1.25 | 1.6 | 4+ | 1.8 | 10.9 | – |
| | 10-9-56 | 39 | 39 | 1.13 | 1.3 | 3+ | 1.5 | 8.0 | 67 |
| | 10-22-56 | 36 | 43 | 1.23 | 0.4 | 4+ | 1.4 | 11.5 | 70 |
| | 12-26-56 | 18 | 25 | 1.26 | 0.4 | 3+ | 1.5 | 14.4 | 43 |
| MG | 6-8-56 | — | 935 | 1.31 | 6.7 | 4+ | 2.4 | 16.6 | 36 |
| | 6-11-56 | — | 1170 | 1.41 | 9.4 | 4+ | 2.7 | 15.1 | 49 |
| | 6-16-56 | — | 1344 | 1.12 | 18.2 | 4+ | 3.9 | 14.8 | 56 |
| | 6-19-56 | — | 1094 | 1.34 | 19.1 | 4+ | 4.1 | 15.4 | 67 |
| | 6-23-56 | — | 644 | 1.28 | 20.0 | 4+ | 3.8 | 14.8 | 41 |
| | 6-26-56 | — | 578 | 1.23 | 16.1 | 4+ | 4.0 | 11.8 | 51 |
| | 7-2-56 | — | 450 | 1.35 | 8.2 | 4+ | 1.6 | 11.0 | 57 |
| | 7-9-56 | 153 | 128 | 1.53 | 7.2 | 3+ | 2.2 | 7.1 | 66 |
| | 7-16-56 | 72 | 37 | 1.55 | 3.2 | 4+ | 1.6 | 6.3 | 72 |
| | 7-24-56 | 30 | 13 | 1.57 | 2.1 | 4+ | 1.3 | 5.6 | 67 |
| | 8-3-56 | 15 | 15 | 1.44 | 2.4 | 3+ | 0.8 | 6.8 | 69 |
| | 8-17-56 | 9 | 13 | 1.47 | 1.4 | 3+ | 0.6 | 6.9 | 55 |
| | 10-29-56 | 7 | — | 1.20 | 0.2 | 2+ | 0.5 | 4.8 | 73 |
| MW | 10-3-56 | 486 | 166 | 1.80 | 3.7 | 4+ | 2.1 | 12.2 | 62 |
| | 10-6-56 | 213 | 58 | 1.97 | 2.7 | 4+ | 1.9 | 10.9 | 56 |
| | 10-12-56 | 77 | 32 | 1.58 | 1.4 | 4+ | 1.7 | 9.6 | 74 |
| | 12-19-56 | 11 | 11 | 2.32 | 0.6 | 2+ | 0.8 | 7.0 | 77 |
| CB | 8-3-56 | 338 | 102 | — | 0.2 | – | – | – | – |
| | 8-6-56 | 298 | 96 | 1.80 | 0.2 | 4+ | 0.7 | 8.2 | 54 |
| | 8-15-56 | 375 | 91 | 1.64 | 0.5 | 4+ | 0.8 | 8.5 | – |
| | 8-29-56 | 354 | 184 | 1.73 | 0.2 | 4+ | 1.1 | 8.4 | – |
| | 9-5-56 | 410 | 267 | 1.68 | 0.5 | 4+ | 1.2 | – | – |
| | 9-10-56 | 515 | 163 | 2.12 | 0.8 | 4+ | 1.0 | 10.3 | – |
| | 9-19-56 | 167 | 82 | — | 0.4 | 3+ | 1.3 | 7.1 | – |
| | 9-26-56 | 65 | 37 | 2.56 | 0.5 | 3+ | 0.8 | 5.3 | – |
| | 10-4-56 | 36 | 25 | — | 0.5 | 0 | 0.5 | – | – |

TABLE 2 (Cont.)
INFECTIOUS HEPATITIS

| *Patient* | *Date* | *SGP-T* | *SGO-T* | *Serum ChE* | *Bilirubin* | *Ceph. Flocc.* | *Thymol Turb.* | *Alk. Phosphatase* | *% Chol. esters* |
|---|---|---|---|---|---|---|---|---|---|
| | | UNITS | UNITS | UNITS | MG/100 ML | | UNITS | UNITS | |
| SBU | 12-26-56 | 846 | 102 | 1.36 | 5.3 | 4+ | 0.4 | 15.3 | 62 |
| | 1-16-57 | 22 | 27 | 1.67 | 1.8 | 1+ | 0 | 7.2 | 71 |
| NB | 1-14-57 | 1163 | 1196 | — | 7.3 | 4+ | 1.9 | 14.2 | – |
| | 1-17-57 | 1093 | 553 | 1.64 | 11.1 | 4+ | 1.4 | 14.4 | 26 |
| | 1-22-57 | 1325 | 1258 | 1.23 | 19.4 | 4+ | 2.5 | 11.9 | 26 |
| | 1-29-57 | 1917 | 1592 | 1.27 | 28.8 | 4+ | 2.8 | 12.8 | 43 |
| WS | 9-27-56 | 1125 | 365 | 1.64 | 8.2 | 3+ | 0.2 | 32.6* | 43 |
| | 10-1-56 | 1075 | 257 | 1.67 | 4.8 | 3+ | 0.2 | 27.9 | 66 |
| | 10-5-56 | 739 | 216 | 1.66 | 3.0 | 1+ | 0.2 | 24.9 | 62 |
| | 10-15-56 | 705 | 172 | 1.90 | 2.4 | 3+ | 0.6 | 23.2 | 83 |
| | 10-22-56 | 508 | 165 | 1.81 | 1.4 | 4+ | 0.3 | 21.7 | – |
| | 11-5-56 | 215 | — | 2.22 | 1.0 | 4+ | 0.4 | 25.4 | – |
| | 11-19-56 | 131 | 68 | 2.43 | 0.7 | 4+ | 0.2 | 24.9 | – |
| | 12-3-56 | 81 | 72 | 2.24 | 1.0 | 3+ | 0.3 | 28.8 | 61 |
| | 12-28-56 | 59 | 50 | 2.01 | 0.7 | 0 | 0 | 27.4 | 57 |
| | * Male, age 14 (Normal range of alkaline phosphatase in children, 10-20 units). | | | | | | | | |
| Healthy Controls | No. | 37 | 77 | 125 | 126 | 100 | 108 | 78 | 84 |
| | Range | 5.5-22.5 | 8.5-29.2 | 1.50-3.00 | 0-1.0 | 0-1+ | 0-1.0 | 2.15-10.4 | 65-80 |
| | Mean | 12.1 | 14.6 | 2.32 | 0.44 | 0 | 0.60 | 5.48 | 75 |

TABLE 3
HEPATOBILIARY DISEASES OTHER THAN INFECTIOUS HEPATITIS

| *Patient* | *Diagnosis and Remarks* | *Date* | *SGP-T* | *SGO-T* | *Serum ChE* | *Bilirubin* | *Ceph. Flocc.* | *Thymol Turb.* | *Alk. Phosphatase* | *Total Chol.* | *% Chol. esters* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | UNITS | UNITS | UNITS | MG/100 ML | | UNITS | UNITS | MG/100 ML | |
| SC | Infectious mononucleosis with liver involvement. ACTH given 4-20 through 4-30-56 | 4-19-56 | – | 173 | 2.82 | 1.6 | 4+ | 1.8 | 22.9 | | |
| | | 4-21-56 | – | 67 | 2.60 | 1.4 | 4+ | 3.3 | 23.3 | | |
| | | 4-24-56 | – | 46 | 2.41 | 0.2 | 4+ | 2.9 | 21.8 | | |
| | | 5-1-56 | – | 23 | 2.62 | 0.5 | 3+ | 2.4 | 11.5 | | |
| NJ | Chlorpromazine jaundice, discontinued 11-6-56 | 11-7-56 | 262 | 110 | 1.57 | 3.2 | 0 | 0.3 | 21.6 | | |
| | | 11-12-56 | 193 | 91 | 1.64 | 1.6 | 1+ | 0.3 | 22.9 | | |
| DB | Chlorpromazine jaundice, discontinued 1-10-57 | 1-10-57 | 455 | 340 | 2.10 | 1.2 | 3+ | 0.4 | 19.8 | | |
| | | 1-14-57 | 157 | 57 | 2.07 | 0.2 | 1+ | 0.6 | 34.2 | | |
| NV | Chlorpromazine jaundice, discontinued 9-21-56 | 9-24-56 | 130 | 76 | 2.08 | 1.3 | 1+ | 0.6 | 28.5 | | |
| | | 9-29-56 | 33 | 51 | 2.23 | 0.8 | 0 | 0.6 | 39.0 | | |
| | | 11-12-56 | 10 | – | 2.48 | 0 | 4+ | 0.7 | 9.6 | | |
| PB | Malignant hypertension with toxic hepatitis from medication | 6-23-56 | – | 451 | 2.68 | 1.2 | 1+ | 0.2 | 15.4 | | |
| | | 6-28-56 | – | 29 | 2.70 | 0.2 | 0 | 0.6 | 9.8 | | |
| | | 10-24-56 | 138 | 114 | 2.62 | 0.2 | 1+ | 0.3 | 12.2 | | |
| | | 10-26-56 | 76 | 34 | 2.70 | 0.3 | 2+ | 0.4 | 9.0 | | |
| | | 11-5-56 | 16 | – | 3.36 | 0.6 | 3+ | 0.6 | 10.0 | | |
| | | 11-26-56 | 9 | 8 | 3.26 | 0.2 | 2+ | 0.4 | 7.5 | | |
| | | 1-9-57 | 10 | 14 | 3.38 | 0.2 | 2+ | 0.4 | 7.9 | | |
| MH | Paracentesis 11-2-56. Deceased 11-4-56, amebic abscess of liver found at autopsy. | 10-19-56 | – | – | 0.83 | 0.2 | 1+ | 0.7 | 16.6 | 116 | 45 |
| | | 10-29-56 | 81 | 130 | – | – | – | – | – | – | – |
| | | 11-1-56 | 66 | 83 | 0.48 | 2.6 | 3+ | 0.6 | 27.3 | 86 | 31 |
| | | 11-2-56 | 63 | 83 | 0.54 | 4.1 | 2+ | 0.6 | 25.3 | 66 | 23 |
| | | | | | | | | | | *Acid phosphatase* | |
| CB | Ca of prostate. 100 mg. i.m. testosterone propionate given/day 5-7 to 5-9-56, inclusive. Bilateral orchiectomy 5-11-56. Stilbesterol 5-18-56 to 8-15-56, inclusive. | 5-2-56 | – | 42 | 1.61 | – | 0 | 0.1 | 22.9 | 17.0* | |
| | | 5-4-56 | – | 57 | 2.02 | – | 0 | 0.1 | 25.3 | 22.4 | |
| | | 5-7-56 | – | 75 | 1.62 | 0.4 | 0 | 0.1 | 29.2 | 13.5 | |
| | | 5-9-56 | – | 78 | 1.61 | 0.2 | 0 | 0 | 25.6 | 29.5 | |
| | | 5-11-56 | – | 84 | 1.47 | 0.1 | 0 | 0.2 | 24.4 | 17.6 | |
| | | 5-12-56 | – | 97 | 1.42 | 0.2 | 0 | 0.1 | 22.2 | 11.3 | |
| | | 5-14-56 | – | 108 | 1.49 | 0.6 | 3+ | – | 18.2 | 6.9 | |
| | | 5-18-56 | – | 129 | 1.09 | 0.8 | 0 | 0 | 26.3 | 2.2 | |
| | | 5-24-56 | – | 52 | 1.06 | 0.4 | 0 | 0.1 | 16.5 | 0.8 | |
| | | 8-15-56 | 8 | 6 | 1.43 | 0.1 | 2+ | 0.2 | 11.6 | 0.6 | |

* Acid phosphatase—maximum normal value 1.0 unit.

TABLE 3 (Cont.)
HEPATOBILIARY DISEASES OTHER THAN INFECTIOUS HEPATITIS

| *Patient* | *Diagnosis and Remarks* | *Date* | *SGP-T* | *SGO-T* | *Serum ChE* | *Bilirubin* | *Ceph. Flocc.* | *Thymol Turb.* | *Alk. Phosphatase* | *Total Chol.* | *% Chol. esters* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | UNITS | UNITS | UNITS | MG/100 ML | | UNITS | UNITS | MG/100 ML | |
| DF | Cirrhosis. Deceased this date | 3-31-56 | – | 381 | 1.24 | 4.8 | 3+ | 0.2 | 5.2 | 209 | 55 |
| AV | Cirrhosis | 5-11-56 | – | 58 | 3.56 | 0.2 | 1+ | 0.1 | 9.1 | 304 | 73 |
| LR | Cirrhosis | 10-10-56 | 28 | 77 | 2.25 | 1.8 | 4+ | 1.3 | 10.0 | 213 | 69 |
| SE | Obstructive jaundice with chronic pancreatitis. 6-21-56, choledocholithotomy, choledochostomy dilatation sphincter of Oddi. | 6-7-56 | – | 139 | 2.12 | 5.1 | 3+ | 2.1 | 24.2 | 270 | |
| | | 6-12-56 | – | 88 | 2.17 | 2.1 | 1+ | 1.3 | 17.5 | 269 | |
| | | 6-18-56 | – | 230 | 1.96 | 2.6 | 4+ | 1.2 | 21.2 | 212 | |
| | | 6-20-56 | – | 82 | 1.64 | 6.4 | 2+ | 1.3 | 22.8 | 264 | |
| | | 6-22-56 | – | 70 | 1.74 | 7.7 | 0 | 1.4 | 19.2 | 264 | |
| | | 6-23-56 | – | 67 | 1.42 | 5.0 | 2+ | – | 15.6 | – | |
| | | 6-25-56 | – | 93 | 1.41 | 3.3 | 2+ | 1.0 | 13.9 | 206 | |
| | | 6-27-56 | – | 81 | 1.61 | 3.8 | 0 | 1.1 | 9.5 | 202 | |
| | | 7-2-56 | – | 62 | 1.33 | 2.3 | 3+ | 1.1 | 15.4 | 185 | |
| FS | Obstructive jaundice with chronic pancreatitis. 1-3-57, cholecystectomy, removal ampulla of Vater. | 12-10-56 | – | – | – | 11.1 | – | – | – | – | |
| | | 12-13-56 | 192 | – | 1.81 | 11.9 | 0 | 0.1 | 24.6 | 250 | |
| | | 12-17-56 | 88 | – | 1.69 | 14.4 | 0 | 0.3 | 27.2 | 350 | |
| | | 12-21-56 | 51 | – | 1.68 | 9.6 | 0 | 0.3 | 22.2 | 269 | |
| | | 12-27-56 | 58 | 53 | 1.50 | 7.6 | 1+ | 0.1 | 22.4 | 273 | |
| | | 1-5-57 | 36 | 32 | 1.05 | 7.2 | 2+ | 0 | 9.0 | 160 | |
| | | 1-7-57 | – | – | 0.91 | 6.8 | 1+ | 0.1 | 9.3 | 185 | |
| | | 1-11-57 | 35 | 45 | 1.13 | 7.9 | 1+ | 0 | 13.1 | – | |
| SW | Acute cholecystitis, cholelithiasis, choledocholithiasis, cholangitis. Surgery 8-29-56. | 8-27-56 | 75 | 113 | 1.53 | 3.2 | 3+ | 0.3 | 14.2 | 150 | |
| Healthy Controls | | No. | 37 | 77 | 125 | 126 | 100 | 108 | 78 | 84 | 84 |
| | | Range | 5.5-22.5 | 8.5-29.2 | 1.50-3.00 | 0-1.0 | 0-1+ | 0-1.0 0.60 | 2.15-10.4 | 149-361 | 65-80 |
| | | Mean | 12.1 | 14.6 | 2.32 | 0.44 | 0 | | 5.48 | 233 | 75 |

after toxic effects of the medication were suspected. Serum bilirubin was only slightly elevated in all three. Serum alkaline phosphatase values were about twice normal, and the results of other tests, such as thymol turbidity, cephalin flocculation and cholinesterase, were not remarkable. SGP-T values were elevated 10 to 20 times normal, and SGO-T activities were two to eight times normal. With discontinuation of the drug, transaminase values began to fall rapidly. The patients were not available for further studies during the recovery period.

Patient P.B. with malignant hypertension is, of necessity, maintained on large doses of 1-hydrazinophthalazine hydrochloride (Apresoline). He was admitted to the hospital with toxic hepatitis on June 22, 1956. SGO-T was 451 units at that time. SGP-T activity was not determined. The only other liver function tests indicating abnormality were bilirubin, 1.2 mg/100 ml., and a slight elevation of alkaline phosphatase. SGO-T was within normal limits in five days. Since this episode, the patient has been followed at about monthly intervals by transaminase determinations. In samples in which both SGP-T and SGO-T determinations were done, SGP-T was the more affected.

M.H., a patient at the Winfield State Training School, was under treatment for amebiasis and macrocytic anemia at the time the first biochemical studies were done, October 19, 1956. In addition to the data given in Table 3, serum albumin values are pertinent to the problem. The values were 3.08, 2.71, and 2.40 gm/100 ml. on October 19, November 1, and November 2, respectively. The low serum total cholesterol values, low per cent cholesterol esters and low serum cholinesterase values are further evidence of the chronicity of the liver disease. An abdominal mass with fluid developed. Exploration was undertaken on November 2, but the only procedure carried out was removal of the abdominal fluid. The patient died two days later, and the abdominal mass at autopsy was found to be an amebic abscess of the liver. On the three occasions that serum alkaline phosphatase was measured, the values were moderately elevated. That serum alkaline phosphatase is elevated in amebic abscess of the liver has been reported by Brem.[16] The laboratory data was of no help in establishing a diagnosis in M.H. However, a pattern of elevated alkaline phosphatase and elevated SGO-T and SGP-T activity, without abnormal bilirubin, thymol turbidity, or cephalin flocculation, will be watched for in individuals with amebiasis.

Patient C.B. was admitted to the hospital for diagnosis. The first biochemical studies on May 2, 1956, were compatible with the diagnosis of carcinoma of the prostate. Serum acid phosphatase by the Fishman method[17] was 17.0 units (maximum normal is 1.0 units). Alkaline phosphatase was also elevated to 22.9 King-Armstrong units. SGO-T was only slightly elevated with an initial value of 42. It seemed advisable to learn if the growth was hormone dependent. To determine this, the sex-hormone stimulation test as outlined by Emerson and Jessiman[18] was carried out. The results are assessed by observing the increase in urine calcium excretion and the worsening of subjective symptoms. It was in conjunction with this test that testosterone was given. The results of the test were positive, and bilateral orchiectomy was done on May 11. There was a steady increase in SGO-T activity from the time of admission to the hospital on May 1 to a peak value of 129 units on May 18. Serum cholinesterase was steadily falling as SGO-T rose. Serum acid and alkaline phosphatase started to fall the day after orchiectomy. SGO-T did not drop until after stilbesterol was given. The extent of liver invasion by the malignancy cannot be determined, but the results are given as they may illustrate the value of SGO-T in following a disease in which there may be liver involvement.

Patient D.F. had liver cirrhosis and acute gastric ulcer with hemorrhage for 52 hours before surgery. He died in hepatic coma a short time after gastrectomy. About an hour before death, the serum SGO-T was 381 units. Since no biochemical data is available on this patient before this terminal sample, nothing can be said as to the progression of the disease. Data on the other two patients with cirrhosis, A.V. and L.R., are also meager. Studies in both patients were made at the time when they were recovering from alcoholic bouts. SGO-T values are moderately elevated in each patient. Only in patient L.R. are both SGO-T and SGP-T values available, but in this patient SGO-T was a better index of liver damage than SGP-T.

The last three sets of data in Table 3 are from patients with obstructive jaundice. S.E. was followed pre- and post-surgically by SGO-T and the other tests shown. The pre-operative chemical picture was confused, with thymol turbidity above normal, cephalin flocculation values from 1 plus to 4 plus, and serum total cholesterol values erratic. SGO-T values varied before surgery from 230 to 82 units. These values are much lower than those found in patients with hepatitis. After surgery, SGO-T levels gradually fell. Follow-up studies were not possible after the patient was dismissed from the hospital.

Patient F.S. came under observation earlier in his illness than the patient just discussed. He was followed pre-surgically by SGP-T and the other liver function tests. SGP-T was moderately elevated on admission to the hospital. This moderate elevation of SGP-T to 192 units, along with a bilirubin value

of 11.9 mg/100 ml., negative cephalin flocculation, normal thymol turbidity, and elevated alkaline phosphatase level (24.6 units), is more suggestive of obstructive jaundice than it is of hepatitis. The increase in total cholesterol from 250 to 350 mg/100 ml. in a four-day period at the beginning of the illness was further suggestion of an obstruction in the biliary tract. On January 3, 1957, the patient underwent cholecystectomy, and the ampulla of Vater was removed to relieve the obstruction. No evidence of stones or malignancy was found. It is too early after surgery to have the recovery data, but the obstruction was proved and the findings thus far are of value as they illustrate the relatively slight increases in SGO-T and SGP-T as compared to those observed in infectious hepatitis. Only pre-surgical data is available on the third patient, S.W., but it too illustrates the relatively small increase in transaminase values in obstructive jaundice. SGO-T value is higher than SGP-T.

In our attempt to learn at first hand the type of pathology likely to affect SGO-T, we measured the activity in one serum sample from an accident patient in whom there had been extensive loss of brain tissue. The value observed was 249 units. The patient died a short time after the blood sample had been drawn. Studies on spinal fluid were not done but would have been of interest.

## Discussion

Our first use of SGO-T determinations was in patients with definite or suspected myocardial infarctions. Compared with normals, the moderately elevated SGO-T values of 60 to 100 units obtained 12 to 24 hours after the infarctions were striking. We felt confident in our first suspected cases that there had not been an infarction when normal activity was found 12 to 24 hours after the questionable attack and the electrocardiograms and other diagnostic tests were normal. With continued use of the determinations, we are satisfied that elevations do occur 6 to 12 hours after myocardial necrosis. The serum activity falls to normal two to five days after the accident. This is in agreement with the observations of LaDue and Wroblewski,[1] Steinberg and Ostrow,[3] Kattus, Watanabe, Semenson, and Drell.[19] However, in some patients, it is difficult to estimate the time of infarction with sufficient accuracy to be certain the blood is drawn at the right interval after the attack to catch the peak value. If an elevated value is found, along with other positive diagnostic signs, a diagnosis of acute myocardial infarction may be made with more confidence. However, we have little assurance in a normal value as an indication of the absence of an infarction. This drawback is stressed by White.[20]

The great increase in SGO-T and SGP-T activity and the gradual return to normal with recovery in infectious hepatitis are, by far, the most striking biochemical changes observed in our 10 patients with this disease. Our observations are in agreement with those of Wroblewski and LaDue,[4, 5, 7, 8] Chinsky, Shmagranoff, and Sherry,[2] and White.[20] By the use of serial determinations of serum transaminase, diagnosis and management of hepatitis should materially improve.

Our experiences with the use of SGO-T and SGP-T tests in other diseases of the hepatobiliary system are too limited to elaborate on which of the two enzymes is more sensitive to the particular pathologic process. However, what data we do have agrees with the observations of Wroblewski and LaDue.[8] The sensitivity of SGO-T and SGP-T to the undesirable side effects of some drugs, as chlorpromazine, is proving a valuable means of early detection of toxicity.

In view of our observation of elevated SGO-T in the patient with brain damage, a paper by Wakim and Fleisher[21] should be mentioned. They produced experimental cerebral infarctions in dogs. They observed a marked increase in glutamic oxalacetic transaminase in the cerebrospinal fluid which reached a peak about 100 hours after the infarction and returned to normal in 15 days. The increase was proportional to the severity and extent of the cerebral infarction. In most dogs there was also an increase in the serum enzyme, but the value was not so good an index to brain damage as the cerebrospinal fluid value.

## Summary

We have reported some results of SGO-T and SGP-T determinations in patients with acute myocardial infarctions and diseases of the hepatobiliary system.

SGO-T activity is moderately elevated after necrosis of the myocardium. The serum level does not increase until four to six hours after the attack and usually returns to normal in two to five days. That the elevated SGO-T value persists for such a short time limits the usefulness of the test as a diagnostic aid and as a guide to therapy.

SGO-T and SGP-T determinations were greatly elevated in our 10 patients with infectious hepatitis, SGP-T being more affected than SGO-T. With recovery, the serum transaminase values gradually return to normal and the changes in SGP-T (or SGO-T) more nearly fit the state of recovery of the pa-

tient than any of the other biochemical liver function tests. SGP-T seems to be a sensitive test for toxic hepatitis, as can occur from some medications.

In three patients with obstructive jaundice, SGO-T and SGP-T were moderately elevated. More data is needed before we can assume the usefulness of transaminase determinations in differentiating between hepatocellular and obstructive jaundice, but our preliminary results are encouraging.

All other diseases of the hepatobiliary system studied showed moderate elevation in SGO-T and/or SGP-T. Our series included patients with cirrhosis, amebic abscess of the liver, and infectious mononucleosis with liver involvement.

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The average man on the street needs to know more science today than the teachers knew a generation ago, just to be able to read his newspapers and magazines intelligently. Music, art—those possessions formerly of the fortunate few—now belong to the people. Whatever field of subject matter you name—its content and significance for modern living has doubled, trebled . . . in recent years!

*—Alexander J. Stoddard*

# Toxic Psychosis

## *A Complication of Overdosage of Anti-Obesity Drugs*

**WILLIAM S. SIMPSON, M.D.,** ***Topeka***

For more than 50 years thyroid preparations have been used in the treatment of obesity, and since 1935 amphetamine has been used for the same purpose. Though it is well known that either of these drugs taken in sufficient quantities may produce signs of "nervousness," a review of the literature reveals that few references are made to the development of "nervousness" to a psychotic degree. In the patient reported, intoxication with thyroid extract and amphetamine occurred in the treatment of obesity, the intoxication precipitating a psychosis.

### Case Report

The patient is a 33-year-old divorced woman from a small midwestern city. She voluntarily referred herself to the Topeka State Hospital for treatment. During the preceding five months she had noticed increasing lack of control over her temper, extreme anxiety and tension, and fear that she might do something to harm other people or herself.

The patient's mother, an extremely domineering, over-religious, hostile, rejecting person, was the family disciplinarian, administering frequent beatings to her children. In contrast, the father, a kindly, quiet, gentle man, was always good with the children. The patient is said to have had an exceptionally bad temper all her life, but between times was a pleasant, kind, gentle girl. The mother always considered her as difficult to reason with and said that she never had had her daughter under control. The patient had an intense hatred of her mother, but she never fought back for the beatings she received. She was considered "dumb" by her teachers and quit school in grade seven at 15. During her teens she ran away from home frequently and had two illegitimate pregnancies.

She married at age 22, but her husband was soon incarcerated in a penitentiary for forgery. Following his imprisonment, she lived with him until he was again sentenced to the penitentiary, at which time she divorced him. At this time she was 30 years old.

All her life she had been a heavy eater, and approximately four years before admission to the hospital she had consulted her family physician for treatment of obesity, as she weighed close to 300 pounds. She was given a diet and a prescription for reducing tablets. The tablets were of three kinds, to be taken at different times of the day. The before-breakfast tablet contained meth-amphetamine hydrochloride 10 mgm., thyroid extract gr. 1, atropine gr. 1/360, and alloin gr. ¼. The before-lunch tablet contained the same ingredients as the first, except that the alloin was omitted. The 4:00 p.m. tablet contained meth-amphetamine 10 mgm., thyroid extract gr. 1, and phenobarbital gr. ¼. After about 18 months her weight had dropped to 170 pounds. She tried stopping the tablets temporarily but found that she immediately gained weight, so she continued taking the tablets regularly three times daily till her admission to the hospital.

**In the case reported, the patient suffered toxic psychosis as a result of the combination of Benzedrine and thyroid administered in treatment of obesity. The literature is briefly reviewed.**

About one year prior to her admission she began to notice slight heat intolerance, mild weakness, fatigability, and palpitation. Gradually and insidiously these symptoms became more pronounced, and she began to notice "nervousness," tremulousness, and feelings of tension.

Five months prior to admission she was operated on for removal of a small tumor of the buttock, under local anesthesia. The tumor was more difficult to remove than the surgeon had expected, and during the latter part of the operation the effect of the anesthetic had worn off, so the surgical manipulations caused her considerable pain. In addition, her convalescence was prolonged because of poor healing. During the convalescence the nervous symptoms suddenly became heightened and continued to increase in severity from that time forward. She became extremely anxious and tense, and the heat intolerance became severe. The slightest effort would cause her to sweat freely. Palpitation, shortness of breath on exertion, and generalized weakness became intensified, and severe insomnia appeared.

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About this time a friend noted that occasionally she would "talk to herself." Once she went over to the corner of her room and talked to an imaginary person. On another occasion she imagined that there were prowlers in her room. Following these events the patient had no recollection of them.

Her violent temper became vicious and almost uncontrollable. Though she had previously been deferential to her mother to the point of obsequiousness, on one occasion she struck her mother. Though she professed to love her boy friend, about two months prior to admission she threatened to kill him with a knife. Immediately following these outbursts, she felt guilty and was frightened to think that such impulses could gain control over her. She became mildly depressed and talked about the possibility of suicide. Her symptoms increased in severity. She began to feel that she should enter a mental hospital and receive treatment, so she had herself committed.

Physical examination showed a stockily built woman who appeared older than her 33 years. She was 5 feet 6 inches tall and weighed 176 pounds. Extreme anxiety, tension, and heat intolerance were evident. Even in a cool room her body was constantly covered with sweat. Her hands were warm and moist. She could walk up and down steps with difficulty, breathing heavily. The extended hands showed a fine fast tremor. The eyes were staring and bright, blinking was infrequent, and a marked degree of lid-lag was present. A mild degree of exophthalmos was present bilaterally. The pupils were widely dilated. The pulse varied between 92 and 104, and the blood pressure was 154/90. The thyroid gland was of normal size.

X-rays of the upper sternal area showed no evidence of an enlarged retrosternal thyroid gland. Blood cholesterol was 260 mgms. per cent. Basal metabolism readings showed results of –14 and +2. Blood Wassermann was negative. Red blood count was 5,400,000, white blood count 8,500, diff. polys 58 per cent, lymphs 42 per cent. Routine urinalysis was essentially normal.

Psychiatric examination showed an extremely anxious, tense, apprehensive woman with a marked startle-reaction. Irritability was pronounced, along with frequent lapses into tears, followed by apologies for her lack of emotional control. She exhibited rage reactions at any fancied slight, out of all proportion to the stimulus. If a letter from her boy friend didn't arrive on the day that she expected it, she would be plunged into depression and would think that he no longer cared for her, that he had found someone else, and so forth. At the receipt of a letter, all these feelings would disappear and she would be "on top of the world." She had a most intense fear that she might do some harm to others, as she knew that her temper was almost beyond control.

The drugs, however, were withdrawn on her arrival (she had even taken a tablet in the morning, before being admitted). In the ensuing three weeks, the change in her symptoms and signs was dramatic. During this time the heat intolerance, sweating, extreme anxiety, insomnia, tension, weakness, tachycardia, hypertension, and eye signs all but disappeared. She asked to be allowed to work on the ward, and she performed the work easily and efficiently. Blood pressure was 120/70, and the pulse was 70. The emotional lability continued, but in an attenuated form.

Psychological tests three weeks after admission showed immaturity, dependency, orality, denial, evasion, strong repressive tendencies, and inability to tolerate anxiety. There were evidences of perceptual and motor disturbances which could be accounted for on the basis of high tension and/or mild organic brain involvement.

About six weeks after admission she was dismissed from the hospital at her own request. Symptoms and signs of the toxic state had disappeared. Though outpatient follow-up was recommended on discharge, she did not come back for further interviews after leaving the hospital.

## Review of the Literature

Much has been written in medical literature regarding the use and abuse of thyroid extract and amphethamine in the treatment of obesity. MacBryde[1] stated that thyroid should be employed only when definite hypothyroidism is present, and then only in amounts sufficient to maintain a normal metabolic rate. Goodman and Gilman[2] question whether it is desirable to produce the symptoms of hyperthyroidism by the use of thyroid when the end result of weight reduction can be obtained by restricting the calorie intake. Moller,[3] Brunn,[4] Lous,[5] and Anderson[6] present a number of cases of thyrotoxicosis which developed following the use of thyroid extract and which did not recede on the removal of the drug. Many of the patients had been given thyroid extract as treatment for obesity. These authors warned that thyroid gland preparations should not be prescribed as a remedy against obesity.

Benzedrine has long been known to have an inhibitory effect on appetite, and MacBryde[1] advocates its use in helping patients control their appetites, giving benzedrine sulphate 5 to 10 mgms. before breakfast and lunch, but not in the afternoon since it causes insomnia.

Goodman and Gilman[2] state that the main results of oral administration of 10 to 30 mgm. of ben-

zedrine are a temporary increase in efficiency, confidence, alertness, and initiative, and elevation of mood, euphoria, elation, lessened fatigue, enhanced motor and speech activity, increased ability to concentrate, irritability, and sleeplessness. They warn, however, that the effects are not always as described, and many patients may complain of headache, palpitation, dizziness, and vasomotor disturbances, or manifest agitation, delirium, depression, or fatigue. Larger doses are always followed by fatigue and mental depression. The reversal of central effects may also follow the continued use of moderate doses. It was noted that restlessness, tremors, insomnia, talkativeness, and irritability are common. Confusion, assaultiveness, hallucinations, delirium, panic states, and suicidal or homicidal tendencies have also been observed, especially in mentally ill patients. They warn that benzedrine should be used with caution in patients with psychopathic personalities and with a history of homicidal or suicidal tendencies. In overdosage,[7] chills, collapse and syncope were noted.

Among the cases of psychosis reported, Norman and Shea[8] report the occurrence of hallucinations, delusions, agitation and resistiveness in a 49-year-old man who had been addicted to benzedrine sulphate for five years. Previous to that, he had been addicted to alcohol. The authors stress that the patient, previous to the addiction, had shown many neurotic traits. The acute psychotic experiences disappeared in about four weeks after cessation of the drugs.

Young and Scoville[9] describe three cases of paranoid psychosis occurring in narcolepsy, two of which appeared to be precipitated by the use of benzedrine. They felt that a careful psychiatric examination is indicated before starting benzedrine therapy on narcoleptic patients, and that if a paranoid trend is discovered, it may be wiser to allow the sleeping spells to continue.

Monroe and Drell[10] report on the oral use of benzedrine from inhalers and note four cases of ideas of reference and hallucinations occurring in the users. They stress that the psychoses exhibited were extensions of latent paranoid trends, and that benzedrine accentuated the trends and resulted in overt psychosis. The symptoms subsided with discontinuance of the drug.

Wallis, McHarg, and Scott[11] report a case of acute psychosis caused by the ingestion of 55 mgm. of dextroamphetamine (the dextrarotatory isomer of racemic amphetamine). There were auditory and visual hallucinations, which disappeared in two days. V. Nandestadh[12] reports a case of psychosis with paranoid delusions in a man who had been addicted to benzedrine for two years. The psychosis disappeared three days after he entered the hospital.

On the other hand, there are reports which indicate that benzedrine may be taken for long periods of time without harm. Bakst[13] reports the case of a man suspected of having narcolepsy, who had been taking 15 to 30 mgm. of benzedrine sulphate daily over a period of approximately nine years. No remarkable effects of the long-continued dosage of the drug could be demonstrated, nor were any perceptible changes noted when the drug was discontinued. Bloomberg[14] found the same results in three patients with narcolepsy who had been taking 70 mgm. or more of amphetamine sulphate daily for 32 months in two cases, and 20 months in one case.

Pelner[15] used a combination of drugs, similar to that used by the woman in the case report above, but each patient was under careful control. He found that after a few months the patient invariably developed tolerance to the drugs and became refractory to benzedrine and atropine. If stopped for about two weeks, the drugs could be started again in smaller doses. He noticed only minor side-reactions and these were rare.

The writer, in perusing the literature, has not been able to find a single case in which both thyroid extract and benzedrine were used simultaneously for the treatment of obesity and which led to the development of a toxic psychosis.

## Discussion

It is evident from the case history presented that the patient had had many longstanding personality difficulties prior to the intoxication with benzedrine and thyroid extract, but that the drugs served to expose latent psychotic tendencies. Though the removal of the drugs caused the overt physical and psychotic manifestations to recede, her potential for psychosis still remained. This observation is in accord with that of others who have observed similar toxic psychoses, in that latent psychotic potentials became manifest. The drugs seemed to have the effect on our patient of over-stimulation, both physically and emotionally, at the same time decreasing the patient's ability to control the expression of latent psychotic tendencies.

It would seem, from the above case report, that there is considerable danger in the use of thyroid extract and amphetamine in the treatment of obesity when the patients are not under careful supervision, and particularly when they show emotional instability and maladjustment prior to the administering of the drugs.

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# Stuttering in Childhood

## *Concepts of Therapy and Results of Research*

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Among the more perplexing problems seen by the general practitioner and specialist is the child who stutters. Customarily a parent of such a child reports having been advised by her doctor to ignore the problem. That this represents far from the optimal solution is reflected by the countless children who continue to stutter in spite of absolute compliance by the parents with this advice. Likewise advice from relatives or neighbors for the child to talk slower, to think before he talks, or to take a deep breath is generally useless. The problem is such that it cannot be ignored by even a well adjusted parent. Adequate treatment by the physician involves knowledge of present research concerning the problem, sources for adequate referral, and acceptance of the patient's complaint as being important.

There have been countless theories and explanations of stuttering for literally thousands of years. Yet today we are essentially confused as to the etiological agent or agents involved. As with most enigmas, proponents of both the psyche and the soma, not to mention those individuals who are a hybrid of both, have advanced proposals. Today, with regard to children who stutter, the ideas of Dr. Wendell Johnson of the University of Iowa have attained the most acceptance. Johnson believes that stuttering in mid and late childhood is related to the child's developmental environment. Studies of children's speech by Davis indicate a wide range of non-fluency. Johnson feels that during childhood there is a possibility for parents to mislabel this normal non-fluency. The child in turn internalizes this label of stuttering and subsequently acquires the stigma and emotional reactions attendant to the label. By the time of the sixth birthday this non-fluency has usually disappeared in most children. Upon this observation the rationale of not directly treating the stuttering of children in their early years is based.

**Today's best results in correction of stuttering are achieved by a combination of psychotherapy and speech therapy. It is unlikely that a patient more than six years of age will grow out of this speech difficulty.**

However, after the child has reached six years of age, the advisability of telling his parents that he will grow out of his difficulty becomes questionable. For it is at this time that the child leaves the home environment and encounters in educational experiences an emotional environment which is not

as understanding as that of the home. Of course the issue is additionally clouded when the patient's home environment is not satisfactory in the beginning.

The numbers of those who have felt the problem to be physiologically based have decreased in recent years. Yet the questions raised by Kopp in his study of the blood chemistry of stutterers, and Orton and Travis in their considerations of cerebral dominance, have not been completely dismissed. Earlier concepts studied and proposed before the advent of present rigorous methodological procedures are currently being re-evaluated.

When a patient is between the ages of 6 to 12, professional help from a speech pathologist can sometimes aid in an early alleviation of the problem. While controversy is present over the basic treatment of the problem among analytically and non-analytically oriented individuals, probably the best results are obtained in those therapies which combine both psychotherapy and speech therapy. As most speech therapists are now oriented, the two approaches are not basically different. In fact overall subgoals and goals of the two are quite similar. Present psychological research does not demonstrate that stuttering in children is the result of nervousness. It does show that many of the extraneous mannerisms commonly seen in the stutterer are his reactions to having difficulty in speaking.

It is most helpful in terms of future rehabilitation if the parents are merely acquainted with available knowledge and the prognosis for their child's rehabilitation. The following statements summarize present research on this problem:

1. More boys than girls stutter. The ratio is approximately 4:1.
2. More of the Caucausian than of the Negro race stutter.
3. Approximately .7 of the population of the United States stutter.
4. It is impossible for the speech pathologist to predict from clinical tests who will make progress in therapy.
5. Stuttering does not occur involuntarily in singing or choral reading. It occurs rarely when talking to animals.
6. There is no one superior method for treatment of the problem.
7. Onset is generally seen prior to adolescence.
8. Perhaps the most consistent fact about the phenomenon is its inconsistency.

If a referral is made to a speech pathologist, it is best to make sure the therapist is a qualified individual as defined by the American Speech and Hearing Association. Referral to clinical psychologists registered with the American Psychological Association is also helpful.

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# THE MONTH IN WASHINGTON

*Editor's Note. The following summary of Washington news was prepared by the Washington office of the A.M.A. for distribution to state and regional medical journals.*

The economy drive to the contrary notwithstanding, health spending by the Department of Health, Education, and Welfare for the fiscal year that began this July already is assured of surpassing last year's record by some $33 million. This assumes, of course, that no further requests will be made by HEW for supplemental funds, a practice common in government for many years.

Research programs were the most favored by legislators, many of whom spoke out against federal spending by other agencies. But when the health budget came up for debate, the economy oratory subsided.

In only one instance was a health program cut back. And to the surprise of many, it occurred in the Senate which traditionally restores budget cuts originating in the House. A sum of $45 million was voted, instead of the House-approved $50 million, for grants to states for sewage treatment works construction. But then the Senate wrote in language permitting states to get their maximum allotments a full year after the fiscal year ends.

The Hill-Burton hospital construction program received $3.8 million less than last year but only because the administration asked for $121.2 million instead of the $125 million appropriated last year.

The National Cancer Institute received the largest dollar increase of any health item in the budget. The increment was $8 million over last year. The administration had asked for $48.4 million, the House voted $46.9 million, and the Senate raised this to $58.5. It was finally compromised at $56.4 million.

Congress obviously agreed with the views expressed by the Senate Appropriations Committee: ". . . the committee is fully aware that it is providing funds for cancer research, the outcome of which is unknown. On the judgment of those who are scientifically most competent, the committee is fully willing to risk the investment on the ground that the chance of a big payoff is a reasonable one. Such risks are inherent in research."

The Institute of Arthritis and Metabolic Diseases fared well, too, getting a total of $20,385,000 compared with last year's $17,885,000. And the Senate Committee charged the institute with taking leadership in research on effects of radiation on the human organism.

The Mental Health Institute's spending has been going steadily upward, and this year it was given another boost with a final appropriation of $39,217,000, an increase of about $4 million. Other research totals for the current year: National Heart Institute, $35,936,000; Neurology and Blindness Institute, $21,387,000; Allergy and Infectious Disease Institute, $17,400,000.

On only one score did the research advocates lose out. The House view prevailed in conference on the setting of a 15 per cent ceiling on additional overhead costs allowed schools and other institutions getting federal grants. This question which drew considerable attention in hearings is likely to be reopened. Congress wants a General Accounting Office study by the end of this year.

In voting a $5 million increase (to $22,592,000) for general public health assistance to the states, Congress was reaffirming its support of helping local health departments increase their professional staffs and broaden their services. The Senate Committee report contained this significant language: ". . . with a population increase of more than 20 million during the past decade, there are no more organized health departments than there were 10 years ago. This means that 18 million people are living in areas with no full-time organized community health services, and millions more live in areas where such services are only fragmentary."

A few days later, the Public Health Service announced plans for a broad survey of rural health needs, particularly in sparsely settled areas. It picked for its first study Kit Carson County, Colorado, an area known for its scattered farm population, low income level, and adverse climatic conditions.

## Capital Notes

The President has signed into law a two-year revision of the doctor draft law permitting selective call-up of physicians to age 35 if they were deferred from regular draft service to complete professional training. . . . The poliomyelitis vaccine act expired July 1 with all but $400,000 of $53.6 million taken up by states for inoculation programs. An estimated 29 million children and pregnant women received 70 million injections. . . . The Public Health Service has conferred with the American Medical Association on medical manpower plans in event of an epidemic of the new Far East influenza. . . . The National Library of Medicine no longer is lending books and other material over the counter to individuals; requests must be channeled through other libraries. . . . The administration bill on federal workers' health insurance has been introduced; it combines both basic and major medical coverage.

# PRESIDENT'S PAGE

Dear Doctor:

The State Board of Healing Arts has been duly appointed, the culmination of years of study, negotiation, and careful planning. On this board will be focused the close attention and great interest of our entire profession and the close scrutiny of other states faced with similar problems. Successful implementation and enforcement of the Healing Arts Act are dependent upon the wisdom and decisions of the board. Therein lies a tremendous responsibility.

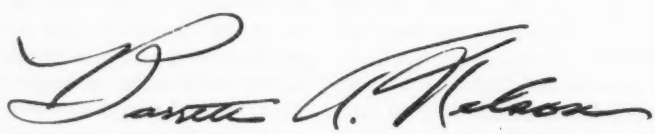
The Kansas Medical Society, having played so large a part in development of the act and in the negotiations with related branches of the healing arts, has a large stake in the future of the board. The Society is convinced that we have a sound law which will properly regulate health practice in Kansas. We can conceive only of successful accomplishment of its purposes.

The osteopathic and chiropractic appointments to the board are most gratifying. The three osteopathic appointees gave full cooperation and worked diligently for the bill in the legislature. They will unquestionably continue to give full cooperation. By fortunate circumstance, the three chiropractic members are from a segment which has earnestly expressed the desire to achieve a smoothly functioning board. Unfortunately, radical elements of their association, those who opposed so viciously in the legislature, are now bitterly attacking the act. They attempted to block the chiropractic appointments and are attacking constitutionality of the act in the courts. However, there is assurance from competent legal advisers that this action will be as futile as were their efforts to stop the appointments by a restraining order.

The five doctors of medicine were appointed by the governor from a list carefully prepared with aid and advice of the Council, the executive committee, past presidents, and a group of interested members. Careful consideration was given to all factors that appeared to influence the composition of a good board. We have confidence in those appointed. They are competent, conscientious, loyal members of our profession. They have undoubtedly familiarized themselves with the details of the act and will shortly partake in preparation of regulations and routines of procedure.

There is extremely keen disappointment that the governor did not see fit to appoint at least one or two members of the retiring board. It is time-honored practice to maintain some continuity on boards and standing committees, to utilize knowledge, experience, familiarity with routine and details which can come only by active participation. The tasks of the board will be immeasurably more difficult; progress and efficiency will be much delayed; there will be many things learned only by making unfortunate mistakes, mistakes which past experience would obviate. However, our board members, being men of intelligence and good judgment, will surely comprehend this and will not fail to turn for counsel to their friends who have served and learned by having met the board's intricate problems again and again.

*Fraternally yours,*



*President*

# EDITORIAL COMMENT

## The Healing Arts Act

As of July 1, the practice acts governing medicine, osteopathy, and chiropractic in the state of Kansas were repealed and a new healing arts board, composed of members of each of those professions, replaced the three previous boards. Below is a summary of the most important sections from the 92 sections comprising the new Healing Arts Act.

SECTION 1. Recognizing that the practice of the healing arts is a privilege granted by legislative authority and is not a natural right of individuals, it is deemed necessary as a matter of policy in the interests of public health, safety and welfare, to provide laws and provisions covering the granting of that privilege and its subsequent use, control and regulation to the end that the public shall be properly protected against unprofessional, improper, unauthorized and unqualified practice of the healing arts and from unprofessional conduct by persons licensed to practice under this act.

SECTION 2. The healing arts include any system, treatment, operation, diagnosis, prescription, or practice for the ascertainment, cure, relief, palliation, adjustment, or correction of any human disease, ailment, deformity, or injury, and includes specifically but not by way of limitation the practice of medicine and surgery; the practice of osteopathy; and the practice of chiropractic.

SECTION 4. No person shall be licensed under this act until he shall have furnished satisfactory evidence to the board that he has attained the age of 21 years, is of good moral character, and a citizen of the United States.

In Sections 9, 10, and 11 the act states that licenses expire on June 30 of each year and may be renewed without examination. If renewal is not accomplished within 30 days thereafter, the license shall be suspended until an additional fee of five dollars has been paid. After 90 days, a revocation order shall be issued, and reinstatement can be accomplished only upon recommendation of the board. The license shall be recorded in the office of the county clerk of the county in which the practitioner practices or resides and, if all other requirements have been met, one temporary permit may be issued prior to the issuance of a regular license.

Beginning with Section 12 the act provides that the governor shall appoint a healing arts board consisting of five members who hold a degree of doctor of medicine from an accredited medical school and shall be residents of Kansas and have been actively engaged in the practice of medicine and surgery in the state of Kansas under licenses issued in this state for a period of at least six consecutive years immediately preceding their appointment. Three shall be osteopathic physicians and three chiropractors, each with similar residence requirements. Appointments after the first time shall be for four years, and no board member may serve more than three consecutive terms. Each shall serve until his successor is appointed and qualified. The governor shall appoint from a list of three names for each vacancy submitted by the professional society involved.

The board shall elect officers, accredit colleges, employ a secretary at a salary of not more than $3,000, and shall have seven persons present at each meeting for a quorum.

SECTION 26. The sessions for the purpose of giving examinations shall be held at such times and places as the board may fix and not to exceed four in any one year.

SECTION 29. All examinations shall be in writing, and the identity of persons taking the same shall not be disclosed upon the examination paper in such a way as to enable the board to know by whom written.

SECTION 30. The examination under this act shall be prepared, given, and graded by members of the board who hold a license similar to that sought by the applicant.

Licenses may be issued by endorsement, as described in Section 33, if the applicant holds a license in some other state where their individual qualifications meet the Kansas legal requirements and he has been in active practice in the previous state not less than one year.

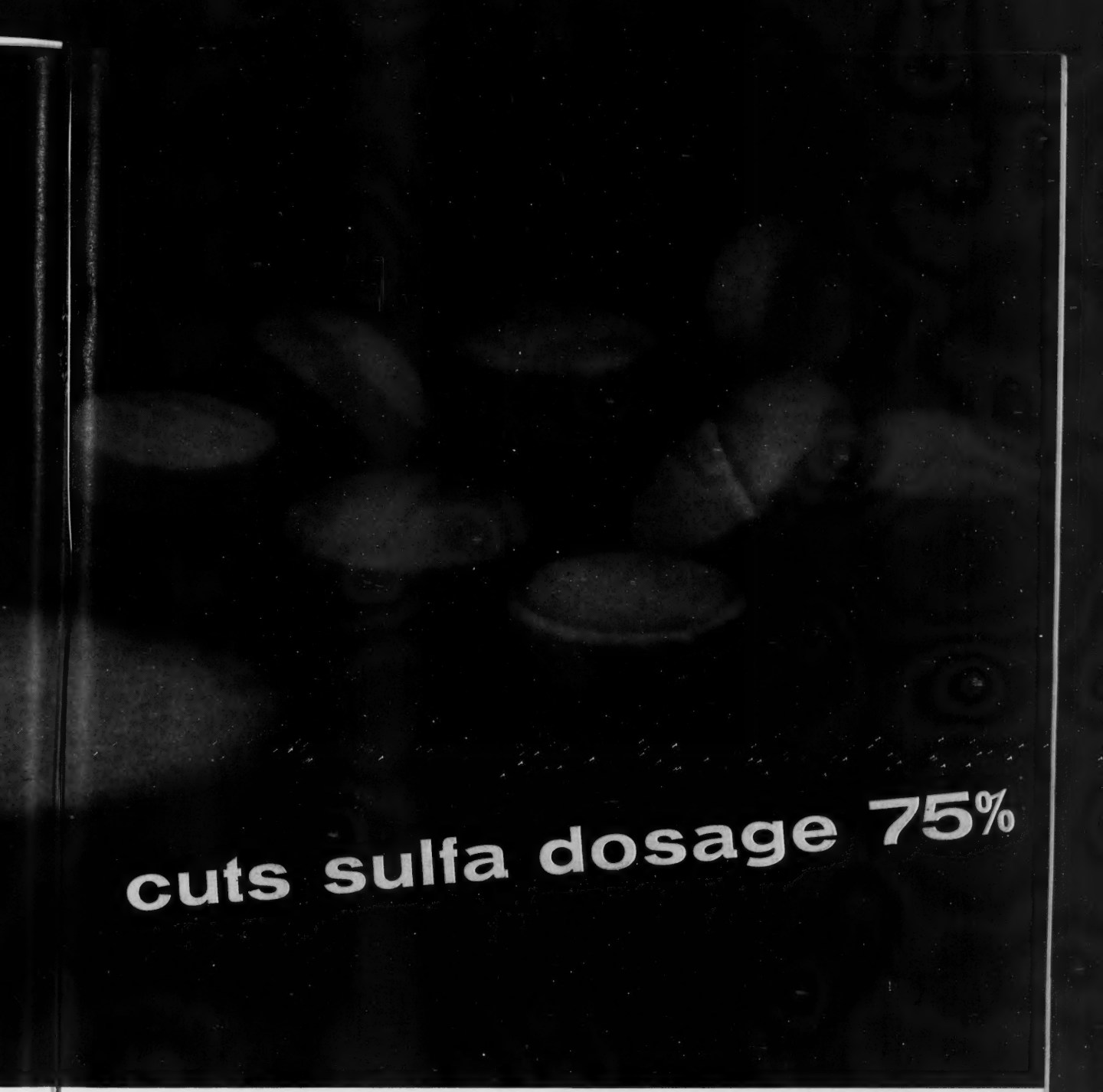
SECTION 36. A license may be revoked or suspended when the licensee is guilty of any of the following acts or offenses: *(a)* Fraud in securing the license. *(b)* Immoral, unprofessional or dishonorable conduct. *(c)* Conviction of a felony. *(d)* Use of untruthful or improbable statements or flamboyant, exaggerated or extravagant claims in advertisements concerning such licensee's professional excellence or abilities. *(e)* Use and distribution of literature advertising professional abilities. *(f)* Other unethical advertising practice. *(g)* Addiction to or distribution of intoxicating liquors or drugs for any other than lawful purposes. *(h)* Willful or repeated violation of this act or the rules and regulations of the state board of health. *(i)* Unlawful invasion of the field of practice of any branch of the healing arts in which the licensee is not licensed to practice. *(j)* Failure to pay annual renewal fees specified in this act. *(k)* Failure to take some form of postgraduate work each year as required by the board.

SECTION 37. For the purpose of the preceding section, "unprofessional conduct" shall consist of any of

**24 hour therapeutic**

**blood levels with**

**a single (1 Gm.) dose**




KYNEX Sulfamethoxypyridazine, the new, long-acting sulfonamide, now enables the physician to attain more effective sulfa therapy with these unequaled clinical advantages—

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**TABLETS:** Each tablet contains 0.5 Gm. (7½ grains) of sulfamethoxypyridazine. Bottles of 24 and 100.

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(1) Boger, W. P.; Strickland, C. S. and Gylfe, J. M.: Antibiot. Med. & Clin. Ther. 3:378 (Nov.) 1956.

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the following acts: *(a)* Solicitation of professional patronage, or profiting by the acts of those representing themselves to be agents of the licensee. *(b)* Receipt of fees on the assurance that a manifestly incurable disease can be permanently cured. *(c)* Assisting in the care or treatment of a patient without the consent of said patient, his attending physician or his legal representatives. *(d)* The use of any letters, words, or terms, as an affix, on stationery, in advertisements, or otherwise indicating that such person is entitled to practice a branch of the healing arts for which he is not licensed. *(e)* Performing, procuring or aiding and abetting in the performance or procurement of a criminal abortion. *(f)* Willful betrayal of confidential information. *(g)* Making use of any advertising statements of a character tending to deceive or mislead the public. *(h)* Advertising professional superiority or the performance of professional services in a superior manner. *(i)* Advertising prices for professional service. *(j)* Advertising by means of a large display, lights, signs, or containing as a part thereof, the representation of any portion of the human body. *(k)* Employing or making use of advertising solicitors or free public press agents. *(l)* Advertising any free professional services or free examination. *(m)* Offering discounts or inducements to prospective patients by means of coupons or otherwise to perform professional services during the given period of time or during any period of time for a lesser or more attractive price. *(n)* Advertising to guarantee any professional service or to perform any operation painlessly. *(o)* Individually advertising any price or prices of corrective devices or services.

The 30 sections following deal with proceedings for suspension and revocation of licenses and spell out procedures necessary to enforce the act and the penalties that may be assessed by the courts for various violations.

SECTION 68. For the purpose of this act the following classes or persons shall be deemed to be engaged in the practice of the healing arts: Persons who hold themselves out to the public as being engaged in or who maintain an office for the practice of the healing arts as defined in section 2 of this act.

SECTION 69. For the purpose of this act the following classes or persons shall be deemed to be engaged in the practice of medicine and surgery: *(a)* Persons who publicly profess to be physicians or surgeons or publicly profess to assume the duties incident to the practice of medicine or surgery or any of their branches.

*(b)* Persons who prescribe, recommend or furnish medicine or drugs, or perform any surgical operation of whatever nature by the use of any surgical instrument, procedure, equipment, or mechanical device for the diagnosis, cure or relief of any wounds, fractures, bodily injury, infirmity, disease or illness of human beings.

*(c)* Persons who attach to their name the title M.D., surgeon, physician, physician and surgeon, or any other word or abbreviation indicating that they are engaged in the treatment or diagnosis of ailments, diseases or injuries of human beings.

In Section 70 the osteopathic physician is defined by the definition hitherto made by the Supreme Court of this state.

SECTION 71. For the purpose of this act the following classes or persons shall be deemed to be engaged in the practice of chiropractic: (1) Persons who examine, analyze and diagnose the human living body, and its diseases by the use of any physical, thermal or manual method and use the x-ray diagnosis and analysis taught in any recognized chiropractic school; and (2) persons who adjust any misplaced tissue of any kind, or nature, manipulate, or treat the human body by manual, mechanical, electrical or natural methods or by the use of physical means, physiotherapy (including light, heat, water or exercise), or by the use of foods, food concentrates, or food extract, or who apply first aid and hygiene, but chiropractors are expressly prohibited from prescribing or administering to any person medicine, or drugs in materia medica, or from performing any surgery, as hereinabove stated or from practicing obstetrics.

SECTION 72. The practice of the healing arts shall not be construed to include the following classes or persons: *(a)* Persons rendering gratuitous services in the case of an emergency.

*(b)* Persons gratuitously administering ordinary household remedies.

*(c)* The members of any church practicing their religious tenets provided they shall not be exempt for complying with all public health regulations of the state.

*(d)* Students while in actual classroom attendance in an accredited healing arts school who after completing one year's study treat diseases under the supervision of a licensed instructor, or while serving an interneship or residency in an accredited hospital.

*(e)* Students upon the completion of at least three years study in an accredited healing arts school and who, as a part of their academic requirements for a degree, serve a preceptorship not to exceed 90 days under the supervision of a licensed practitioner.

*(f)* Persons who massage for the purpose of relaxation, muscle conditioning, or figure improvement, provided no drugs are used and such persons do not hold themselves out to be physicians or healers.

*(g)* Persons whose professional services are per-

formed under the supervision or by order of or referral from a practitioner who is licensed under this act.

*(h)* Persons in the general fields of psychology, education and social work, dealing with the social, psychological and moral well-being of individuals and/or groups provided they do not use drugs and do not hold themselves out to be physicians, surgeons, osteopathic physicians or chiropractors and provided that the state of Kansas does not license their professional activities.

*(i)* Practitioners of the healing arts in the United States army, navy, air force, public health service, and coast guard or other military service when acting in the line of duty in this state.

*(j)* Practitioners of the healing arts licensed in another state when and while incidentally called into this state in consultation with practitioners licensed in this state, or residing on the border of a neighboring state, duly licensed under the laws thereof to practice a branch of the healing arts, but who do not open an office or maintain or appoint a place to regularly meet patients or to receive calls within this state.

Dentists, optometrists, nurses, podiatrists, and pharmacists, when practicing their professions, are not included in the provisions of this act.

SECTION 73. *(a)* Each applicant for a license by examination to practice any branch of the healing arts in this state shall: (1) present proof that he is a graduate of an accredited high school. (2) Present to the board a certificate of ability in anatomy, physiology, chemistry, bacteriology, and pathology issued by the board of basic science examiners of this or any other state, or territory, or of the District of Columbia. (3) Present proof that he is a graduate of an accredited healing arts school or college. (4) Pass an examination prescribed and conducted by the board covering the subjects incident to the practice of the branch of healing arts for which the applicant applies.

*(b)* Any person seeking a license to practice medicine and surgery shall present proof that he has completed an acceptable internship as the board shall require.

Also in this section is included a provision that osteopaths practicing in Kansas as of January 1, 1957, or who have graduated from an accredited college of osteopathy after June 1, 1950, may take an examination in medicine and surgery and, if successful, shall be given a license entitling them to perform surgery with instruments and to use drugs. The medical segment of the board shall provide refresher courses in the fields of medicine and surgery as an aid to the osteopaths now practicing in Kansas who may wish to take the board examination.

SECTION 74 states that an accredited school of medicine shall have a standard not below that of the University of Kansas School of Medicine. Section 75 states that an accredited school of osteopathy shall have a standard not below that of the Kirksville College of Osteopathy and Surgery. Section 76 states that an accredited school of chiropractic shall have a standard not below that of the National College of Chiropractic of Chicago. All three sections then state that all such schools shall be approved by the board.

SECTION 81. All licenses duly issued prior to the taking effect of this act shall be and continue in full force and effect and be renewed under the provisions hereof.

SECTION 84. All examinations for licensure shall be given only by such members of the board who hold a license in that branch of the healing arts for which the applicant seeks a license, provided that an osteopathic physician seeking a license to practice medicine and surgery shall be examined by those members of the board who hold licenses to so practice.

SECTION 85. No person licensed hereunder shall use a title in connection with his name which in any way represents him as engaged in the practice of any branch of the healing arts for which he holds no license: *Provided, however,* That every such licensee when using the letters or term "Dr." or "Doctor" shall use the appropriate words or letters to identify himself with the particular branch of the healing arts in which he holds a license.

SECTION 92. This act shall take effect and be in force from and after July 1, 1957, and its publication in the statute book.

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## Stormont Medical Library

Loans from the Stormont Medical Library will be sent anywhere in the state. Is that knowledge surprising? Since several physicians have confessed little knowledge about the history and services of this state library, a few pertinent facts are reviewed here. They will be helpful to any physician who wants a bibliography or who needs to refer to the literature for aid in preparing a paper, a case report, a speech.

Requests for material may be mailed to Stormont Medical Library, State House, Topeka, or may be telephoned to Topeka 5-0011, extension 297. Borrowers pay only the cost of postage, and library mailing rates are low, four cents for the first pound and one cent for each additional pound. The usual lending period is for one month.

New medical books are being added continually.

More than 100 medical journals are received by subscription, and an additional 80 are received through gifts, some from the JOURNAL OF THE KANSAS MEDICAL SOCIETY through its exchange agreements with other publications. Patrons are invited to suggest purchases.

The library was established through a gift from Mrs. Jane C. Stormont as a memorial to her husband, Dr. David M. Stormont, who had been devoted to development of medical service and health protection in Kansas throughout his professional life. A small income from the original endowment is still being received, although appropriations from the state legislature provide for the purchase of most books, periodicals, and equipment, and the salary of a full time librarian.

Kansas physicians are urged to use the lending service at any time and to visit the library in its state house quarters. It can serve and expand only through use.

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### Healing Arts Board

The appointment of five members of the Kansas Medical Society to the newly organized Healing Arts Board, as provided by the 1957 legislature, was announced on July 1 by Governor George Docking: Dr. William P. Callahan, Wichita, for four years; Dr. Billens C. Gradinger, Halstead, for four years; Dr. Francis J. Nash, Kansas City, for three years; Dr. Robert Moore, Lansing, for three years; Dr. Louis L. Bresette, Kansas City, for two years.

At the same time the following osteopaths were named to serve on the board: Dr. J. B. Donley, Kingman, for four years; Dr. Richard Gibson, Winfield, for three years, and Dr. Stanley Davis, Columbus, for two years.

The three chiropractic members of the board were not appointed at that time because of legal difficulties but were later announced to be Dr. Joseph Samskay, Kansas City; Dr. L. C. Neff, Topeka, and Dr. C. L. Blattner, Clay Center.

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### Basic Science Board

The names of five Kansans who will serve as examiners in the basic sciences, under provisions of a law passed by the 1957 legislature, were announced recently by Governor George Docking as follows: pathology, Dr. Robert E. Stowell, University of Kansas Medical Center, Kansas City, for a four-year term; physiology, Dr. Edwin Martin, Kansas State Teachers College, Hays, four years; chemistry, Dr. L. C. Heckert, Kansas State Teachers College, Pittsburg, three years; anatomy, Dr. E. J. Wimmer, Kansas State College, Manhattan, two years; bacteriology, Dr. Merle E. Brooks, Kansas State Teachers College, Emporia, one year.

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### Changes in A.M.A. Staff

Two changes in the American Medical Association administrative staff were announced recently. Dr. George F. Lull, who has been secretary-general manager of the association for 11 years, has been elevated to the newly-created position of assistant to the president. He will continue serving as secretary, an elective office.

Dr. F. J. L. Blasingame of Wharton, Texas, will take over the position of general manager on January 1. He has been a member of the A.M.A. Board of Trustees since 1949, was president of the Texas State Medical Association in 1955, and is now serving as president of Blue Cross-Blue Shield Plans of Texas. He has been practicing in Wharton for 20 years.

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### Hurricane Relief Fund

Voluntary contributions are now being received to aid three physicians who lost their offices, clinics, and homes in the Louisiana hurricane late in June. Funds may be sent to Cameron Parish Medical Rehabilitation Fund, c/o Louisiana State Medical Society, Room 105, 1430 Tulane Avenue, New Orleans 12, Louisiana.

All three of the physicians are under 37 years of age, and all are determined to return to their rural practices in the devastated area. One of the three, Dr. C. W. Clark, lost three of his five children in the hurricane.

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Hugo Zee, a senior student at the University of Kansas School of Medicine, is one of 34 undergraduate students selected by the American Psychiatric Association to receive fellowships in psychiatry awarded by the Smith, Kline and French Foundation. He is working this summer in the in-patient department at the University of Kansas Medical Center.

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The manufacture of pharmaceuticals is among the nation's fastest-growing industries. Parke, Davis and Company report there are approximately 1,200 manufacturers and distributors serving nearly 200,000 physicians and 53,000 pharmacies.

# BLUE SHIELD

## Kansas Blue Cross-Blue Shield and Cooperatives

Occasionally you may have heard or have been asked this question. Are Blue Cross-Blue Shield cooperatives? The answer is no. However, to fully appreciate the differences between these plans and cooperatives requires an understanding of the unique role Blue Cross-Blue Shield has in our American economy. It is necessary to know what these organizations are trying to do.

The basic problem these plans are trying to solve is one of providing a way for all segments of the community to finance their health care. Included in all segments are low income groups, the aged, the chronically ill and disabled, as well as the average or good risk group of people. This problem is complicated somewhat by the fact that there is an increasing demand by the public for better hospital and medical services in a rising economy. The basic premise of Blue Cross-Blue Shield is that this problem can be solved *voluntarily* without government control or intervention and at the *local level.* This is consistent with the American way of meeting public needs. Blue Cross-Blue Shield believes that this is not only an economic problem but a social problem as well, one in which the whole community must assume some responsibility.

There are some similarities between Blue Cross-Blue Shield and cooperatives. All insurance is a cooperative enterprise in some respects; members pool resources and share risks equally. Many American business enterprises also employ certain cooperative arrangements to meet certain needs. The American railroad industry, for example, found the need to pool its resources and equipment and eliminate competition in order to handle their express services. As a result, the American Railway Express Company was created. Banks join cooperatively to support, for their own use, the facilities and services of a clearing house. American newspapers have pooled their reporting resources and facilities and established a cooperative enterprise known as the Associated Press.

However, this is really beside the point. Blue Cross-Blue Shield are different from cooperatives in purpose, scope of services, legal status, and methods of operation. Blue Cross-Blue Shield are designed to help all Kansans finance their health care. Services are not limited to any particular occupational group or business or trade association. Legally, there are several important differences. Blue Cross-Blue Shield come under the insurance laws of Kansas and came into existence as a result of special enabling acts passed by the state legislature. They are under the supervision of the state commissioner of insurance. Cooperatives are dependent on the corporation laws of the state for their existence.

Blue Cross-Blue Shield have no profits to distribute to their members because they are non-profit organizations. While there are many different kinds of cooperatives, most divide their profits among their members in proportion to their patronage of the cooperative services or goods. Blue Cross-Blue Shield are limited by statute as to the amount of money they can spend for the administration of the plans. This is not true of most businesses. Not more than 15 per cent of the plans' income can be used for administrative purposes, and not more than 10 per cent can be used for enrollment. Actually, Kansas Blue Cross-Blue Shield have been using approximately 10 per cent of income for administration and enrollment. In addition to this 10 per cent which the plans needs to operate, a small per cent (one to five per cent) is held out for reserve.

This reserve fund differs from a surplus. It is not a fund from which stockholders or owners receive dividends, because there are no owners as such in Blue Cross-Blue Shield. The purpose of the reserve fund is to pay claims during periods of unusually high demand and to help operate the plans when current income is less than expenses. This reserve fund allows Blue Cross-Blue Shield to make an orderly adjustment of dues and experiment with new types of coverage without jeopardizing the rate structure.

Blue Cross and Blue Shield are managed by boards of directors, composed of members, public at large, doctors and hospital people, who serve without pay. There is a salaried staff, headed by an executive director, who carries out the directives of the boards.

In most respects, Blue Cross-Blue Shield resembles a commercial enterprise in its methods of operation. Paying out over $1,000,000 a month in claims requires the most efficient methods of administration. Blue Cross-Blue Shield employs modern business techniques and accounting systems. Flow charts, quality control systems, and the most advanced automatic equipment are all a standard part of its operation. In addition to this, Blue Cross-Blue Shield is assisted in its claims handling by the doctors and hospitals who actually make out claims for members at the time of service. This enables Blue Cross-Blue Shield to handle claims faster and with a minimum of error.

The close relationship between Blue Cross-Blue Shield and the community hospital and doctor gives

these plans the advantage of being more sensitive to the real health needs of the community. It also permits them to develop flexible programs which can be adjusted quickly to changes of the economy.

In some respects, Blue Cross and Blue Shield resemble cooperatives, and in other respects they resemble regular American enterprises. But, Blue Cross-Blue Shield is essentially a unique and special kind of enterprise that was developed to meet a special kind of need. The plans are not cooperatives and they are not commercial enterprises. They are community service organizations whose sole purpose is to serve the interests of the public, doctors, and hospitals.

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### Auxiliary Wins Prize

The Woman's Auxiliary to the Kansas Medical Society placed first among states of its size in a contest closed recently by the Auxiliary to the American Medical Association for the sale of subscriptions to *Today's Health*. Three Kansas county organizations also won prizes.

The state group was awarded a cash prize of $40. Mrs. Francis Basham, Eureka, served as chairman of the *Today's Health* contest for Kansas.

The Auxiliary in Sedgwick County placed first in competition among organizations of its size. Mrs. Paul A. Lovett was chairman. Second prizes in their size groups were won by the Greenwood-Woodson counties organization, Mrs. Robert Obourn, chairman, and by the Labette County Auxiliary, Mrs. A. L. Berggren, chairman.

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### Fellowship for Orthopedic Surgeon

Dr. Charles E. Workman, who completed his fourth year in an orthopedic residency at the University of Kansas School of Medicine last month, was recently awarded a fellowship of $7,330 by the National Foundation for Infantile Paralysis. The money is to be used to assist in an additional year's preparation for teaching and research in orthopedics. Next year Dr. Workman plans to serve as a clinical instructor of orthopedic surgery at the Kansas school.

The study financed by the grant includes work on hand surgery at Northwestern University in Chicago under Dr. Michael L. Mason, techniques in equalizing leg lengths at Marquette University under Dr. Walter P. Blount, and the treatment of scoliosis at the Clinic of Orthopedic Surgery in Pasadena under Dr. Joseph C. Risser.

### Clinical Session in Kansas City

The annual conference of the Kansas City Southwest Clinical Society will be held this year from September 30 through October 3, at the Municipal Auditorium in Kansas City, Missouri. A list of the speakers to take part and announcement of features of the conference may be found in an advertisement on Page 569 of this issue. Physicians who are members of medical societies in the counties in which they reside are invited to attend.

One of the highlights of the program is a symposium, "The Medical Effects of Radiation," to be moderated by Dr. Eugene P. Cronkite, pathologist-hematologist of Upton, New York. When testifying before a Senate-House subcommittee on atomic energy Dr. Cronkite stated his belief that nuclear war would have "unthinkable" results on all living things.

The complete program of the conference will be published in the September issue of the *Kansas City Medical Journal,* to be distributed the first week in September. Copies may be secured from 3036 Gillham Road, Kansas City, Missouri.

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### A.M.A. Studies Chemical Laws

A hodge-podge of state and federal laws regulating the labeling of hazardous chemicals and the need for a uniform chemical law recently were revealed by an American Medical Association study. Sponsored jointly by the A.M.A.'s Committee on Toxicology and Law Department, the study was made in preparation for drafting a model chemical labeling law. A conference of interested representatives of government, industry, and medicine will be called this fall to draft a model law which then can be submitted to legislative bodies.

The proposed legislation is intended to reduce careless and ignorant handling of potentially harmful products in and around the home, small businesses, and other areas where control of over-exposure to chemicals is not as efficient as in the manufacturing process. This law will require informative labeling, including listing of possibly harmful ingredients, their potentialities for danger, directions for safe use, and first-aid instructions.

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Health is expensive, but disease is even more so. Those who have funds to invest in the welfare of the country of tomorrow could do no better than investing them in the welfare of the students of today. —*Dale L. Farnsworth, M.D., Bulletin, N.T.A., May, 1956.*

# Tumor Conference

## *Carcinoma of the Bladder*

**Edited by Robert Qualheim, M.D.**

Dr. Stowell: Tumors of the urinary bladder may have a variable growth behavior including a tendency for multicentric origin and recurrence over a prolonged period of time.

Mr. Arnold (Medical Student): M. B., a 74-year-old white man, was first seen at the University of Kansas Medical Center on October 12, 1956, with a chief complaint of "prostate trouble" of one year's duration.

The illness began one year before when the patient first noted frequency of urination associated with mild dysuria. These symptoms were persistent and became progressively more frequent during the preceding year, and during the preceding month he had had to urinate every 30 minutes. Eight months before he first noted terminal hematuria, and this had occurred three or four times during the preceding month. However, he had not observed the passage of blood clots.

In 1952 he had a diagnosis of a right renal stone, but no recurrence of symptoms had occurred.

Physical examination on admission revealed a well developed but thin elderly man. The positive physical findings were hyperresonance to percussion of the chest, firm bilateral inguinal lymph nodes, and a loss of vibratory sensation in both lower legs. On rectal examination the prostate was somewhat enlarged.

Laboratory examination on admission produced the following results. Specific gravity of the urine was 1.010 with a trace of albumin and an acid reaction. The sediment exhibited many red cells and 14-6 white blood cells per high power field. The red blood count was 4.23 million, and a complete hematologic work-up revealed no evidence of pernicious anemia. Cystometric examination revealed an uninhibited neurogenic bladder.

Dr. Stowell: Dr. Todd, would you discuss the roentgenologic findings, please?

Dr. Todd: By intravenous pyelograms the left kidney shows a normal architecture, but at no time is contrast medium visualized on the right. There is a suggestion of an irregular filling defect at the base of the bladder on the left side, but no obstruction to the ureter is present. However, there is something producing obstruction on the right, and it may be an invading tumor involving the whole bladder, as the urinary bladder is of smaller diameter than usual.

Generally, the radiologist leaves the localization of hematuria from the bladder to the cystoscopist, because he makes a more accurate and logical approach to the problem.

Dr. Helwig: Microscopically the biopsy from the bladder shows a pattern of fronds covered by transitional epithelial cells. The tumor cells are relatively uniform without appreciable atypicality. The sections do not show the base, so we can't say whether or not it is invasive, but it seems to be chiefly superficial overgrowth.

Because of the unpredictability of the future clinical behavior of these so-called benign papillomas, I have long since stopped diagnosing them as benign, and call all of them carcinoma, grade I. Approximately 17-25 per cent of those diagnosed as benign will be followed by carcinoma within a period of five years.[1] It is true that about 75 per cent will be cured, usually by simple fulguration and removal, but the other 25 per cent that recur reveal nothing in their original microscopic pattern that gives one any idea what the subsequent course will be.

Regarding the problem of bladder tumors in general, the pathologist lays great stress not only on the grade of the tumor, but of even more importance, the presence or absence of muscle invasion. It has been shown[2] that the theoretical cure rate of neoplasms of various depths of penetration ranges from 100 per cent of the lesions confined to the mucosa to 86 per cent of those penetrating less than one half of the muscle thickness and then drops to 26 per cent of these that have reached the extravesical tissue. The clinical results, however, are not nearly so encouraging as the above figures would indicate, but they do confirm that once the neoplasm has penetrated past the mid-portion of the muscular layer, the chance of cure drops to a very low percentage.[3]

Dr. Valk: This man's first symptom was vesical irritability manifested by frequency and dysuria, and four months later he noted gross hematuria. Most commonly this sequence is reversed. In a large series

Cancer teaching activities at the University of Kansas Medical Center are aided by grants from the National Cancer Institute, U. S. Public Health Service, and from the Kansas Division of the American Cancer Society. Dr. Qualheim, a Clinical Fellow of the American Cancer Society, died February 7, 1957.

of cases[4] hematuria was the presenting complaint in 68 per cent and vesical irritability in 28 per cent.

Our first diagnostic step was to do an intravenous pyelogram so that we could rather quickly survey the genitourinary tract to see if we could localize the source of his bleeding. The intravenous pyelogram showed a non-functioning kidney on the right side which could well have been the source of his trouble. He was examined by cystoscope the next day, and the biopsy was obtained. The tumor appeared to be more invasive than a carcinoma grade I, and we feel that although the pathologist gives us the final word as to the malignancy of the lesion, the cystoscopist can also judge the malignancy by the size of the base and the fixation of the tumor to the submucosa and muscularis. By this method one may be able to differentiate between the 25 per cent which look like a papilloma but which actually invade the muscularis.

We were surprised that the pathological report was a grade I transitional cell carcinoma, so we took the patient to surgery and with a resectoscope removed all of the tumor.

The tumor presented at the bladder outlet and just into the trigone. There was a mass of tumor over the right ureteral orifice, and this may mean that there has been invasion into the orifice causing the obstruction and the non-functioning of the right kidney. On the other hand, it may be a mechanical block due to the advance of the tumor at that point.

Dr. Donnell: The tumors at the base represent a small proportion of the bladder neoplasms that are amenable to inferior segmental resection for the following reason. The lymphatic drainage of the bladder is primarily in a circumferential manner. The lymphatics of the bladder, draining downward to the nodes of the trigone and base, drain primarily laterally and posteriorly in a segmental fashion. We feel that if we can remove the inferior portion of the bladder, we have not only removed the tumor but also the distal lymphatic bearing tissue, and, by so doing, have done as good an operation as if we had taken the whole bladder. For a satisfactory operative procedure the tumor must be limited to at least the lower half of the baldder and preferably even less than that, because a margin of normal tissue has to be removed with the tumor.

The papilloma of the bladder is an extremely interesting lesion, and some people feel that it is of viral origin. Certainly those who have been trying to cure these lesions by destroying one here, one there, and then three to six months later find a new group of lesions wonder whether or not it hasn't grown too fast to be merely a manifestation of multicentric origin. Such lesions can be produced by some of the aniline dye derivatives such as beta naphthylamine and benzidine. Some people believe that the bladder epithelium may react by metaplasia and then neoplasia to a great number of possible noxious agents that a person ingests.

Dr. Stowell: Dr. Valk, do you wish to comment further about the possibility of substances in the urine reacting upon the bladder epithelium?

Dr. Valk: If the urinary stream is diverted by means of ureterostomies or uretero-rectal anastomoses, and then the patient is exposed to these known carcinogenic agents, papillomas will not develop. This implies that something that is eliminated through the urinary system stimulates the bladder epithelium to proliferate.

Dr. Helwig: It has been found[5] that tryptophane is not metabolized the same way in some patients with papilloma and carcinoma as it is in normal people.

Regarding diversion of the urinary stream, McDonald[6] recently produced beta-naphthylamine cancer of the bladder in dogs and then diverted the urinary flow. He hoped this would cause regression of the carcinomas, but the tumors continued to grow.

Medical Student: Is there incontinence following segmental resection?

Dr. Valk: Although it is a hazard, incontinence of the bladder is infrequent.

Dr. Stowell: This is an interesting example of a bladder tumor which brings up the problems of causal factors, course, and development of such tumors, and the fact that they frequently tend to recur. It is very difficult for the pathologist, who looks at only a small portion of the tumor, to predict the future biologic behavior of such growths. By close cooperation between the surgeon and the pathologist, the true extent and the proper course of therapy can be more readily ascertained. Unless treated adequately during its early development, such a tumor will eventually cause death of the patient.

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# PHYSICIANS' ACTIVITIES

**Dr. Arthur L. Duell,** who recently completed a three-year residency in internal medicine at Baylor University, Houston, has begun practice in Concordia in association with the **Gelvin-Haughey** clinic.

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Plans to practice in Burlington have been announced by **Dr. Ellis Duncan,** former assistant professor of surgery at the University of Louisville School of Medicine. Dr. Duncan, a diplomate of the American Board of Surgery, practiced in Louisville before World War II, then was in the Army until 1945.

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**Dr. Clarence H. Benage,** Pittsburg, will be chairman of a round table session on "Projects for Patient Care, Commissions and Committees" at the annual meeting of the American Hospital Association to be held in Atlantic City on October 3.

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**Dr. Carl C. Gunter** and **Dr. Herman W. Hiesterman,** Quinter, announce that **Dr. Richard L. Penfold** is now associated with them in practice. Dr. Penfold, a 1956 graduate of the University of Kansas School of Medicine, recently completed internship at Kansas City (Missouri) General Hospital.

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The American Heart Association and the Kaw Valley Heart Association announce a grant of $2,450 to **Dr. G. Loren Norris,** of the H. L. Snyder Memorial Research Foundation, Winfield. The amount is to be used on heart research problems.

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A talk on mental health was given by **Dr. Ward M. Cole,** Wellington, at a recent meeting of the Wellington Lions Club.

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**Dr. Arthur M. Dougherty,** formerly of Dodge City, has moved to Ukiah, California, and is now engaged in the practice of industrial medicine there. His office in Dodge City has been taken over by **Dr. Eugene M. Schwartz,** who was graduated from the University of Kansas School of Medicine in 1950. Since then he was in private practice for a time, served in the Army, and completed a residency in ophthalmology at the Indiana University Medical Center, Indianapolis.

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**Dr. Wayne G. Parker,** who was graduated from the University of Kansas School of Medicine in 1956, completed his internship at Methodist Hospital, Indianapolis, last month and is now practicing in Hoxie in association with **Dr. John Neuenschwander.**

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**Dr. Frederick F. Lemon,** Douglass, closed his office last month and will continue practice on a part-time basis from his home. The 82-year-old physician, in Douglass since 1917, began practice 56 years ago in Missouri, moved to Oklahoma for six years, and had an office in Stafford for a year before going to Douglass.

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A 1956 graduate of the University of Kansas School of Medicine, **Dr. Perry U. Hunsley,** returned from Ohio last month, on completion of internship at Akron General Hospital, and began practice in Belleville.

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Plans to open an office in Buhler have been announced by **Dr. O. J. Friesen.**

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**Dr. Wayne L. Fowler,** Concordia, recently became a diplomate of the American Board of Internal Medicine.

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A feature story in the *Hutchinson News-Herald* on June 12 paid tribute to **Dr. John J. Brownlee,** who has completed 46 years of practice there. Although he has not retired, he is restricting his practice.

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**Dr. James H. Davis,** who has been practicing in Council Grove for two years, has begun a residency in surgery at the George Washington University School of Medicine, Washington, D. C. **Dr. Royal A. Barker,** formerly of Peabody, has moved to Council Grove to take over Dr. Davis' practice, in association with **Dr. Robert W. Blackburn.**

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An account of his trip to Russia was given by **Dr. Rene M. Gouldner,** Wichita, when he addressed the Tri-County Medical Society at a meeting held in Harper recently.

# DEATH NOTICES

ARTHUR CORNELIUS GULICK, M.D.

Dr. A. C. Gulick, 88, Goodland physician for 57 years, died at Boothroy Memorial Hospital there on July 4. He had begun practice there immediately after his graduation from Jefferson Medical College, Philadelphia, in 1900. Dr. and Mrs. Gulick had been recognized at a community celebration in 1952 and were presented with numerous gifts and honors, among which was the naming of a city park in their memory. Dr. Gulick had served terms on the Goodland board of education, had been coroner and county health officer for varying periods of time, and had been active in Chamber of Commerce and other community work.

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CLARENCE HORACE KINNAMAN, M.D.

Another 88-year-old physician, Dr. C. H. Kinnaman of Topeka, died on July 9 after a long illness. An honorary member of the Shawnee County Medical Society, Dr. Kinnaman had been associated with the Kansas State Board of Health for 31 years and at the time of his retirement was serving as state epidemiologist. He was graduated from Keokuk Medical College in 1899 and came to Kansas in 1920 to head the health department in Geary County, the first such office in Kansas, sponsored by the Rockefeller Foundation as a demonstration health unit. During World War I he served in the Army medical corps, both in this country and overseas.

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BENJAMIN HARRISON MAYER, M.D.

Dr. B. H. Mayer, 69, who had been ill for several months, died at the Ellsworth Hospital on July 17. He had practiced in Ellsworth since his graduation from Kansas Medical College, Topeka, in 1911, except during World War I when he served in the armed forces. He was an honorary member of the Central Kansas Medical Society. He was the center link in a three-generation medical family and had practiced in Ellsworth with his father, the late Dr. Henry C. Mayer. His son, Dr. B. H. Mayer, Jr., practices in Denver.

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**Dr. Findley Law,** who has been practicing in Bird City, has moved to Ellinwood and is now practicing there.

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**Dr. James M. Stout,** Hutchinson, has been called to active military duty for a period of two years. During his absence **Dr. Marion E. Nunemaker,** Hutchinson, will serve as city health physician.

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On completion of internship at Wesley Hospital, Wichita, on July 1, **Dr. Ross L. Jewell,** a graduate of the University of Kansas School of Medicine, went to St. John to begin practice.

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**Dr. Marvin H. Cheshire,** who had been practicing in Hardtner, went to Winston Salem, North Carolina, last month to begin a three-year residency in surgery.

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The *Inman Review* has announced that **Dr. Willard E. Kaufman** has opened an office there as an extension of his primary office in Moundridge. Dr. Kaufman was graduated from the University of Kansas School of Medicine in 1953, served an internship at Wesley Hospital, Wichita, and then practiced in the Holy Land under the Mennonite Central Committee for two years. He recently completed a general practice residency in the Sedgwick County Hospital, Wichita.

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**Dr. Lewis L. Robbins,** Topeka, was one of the guest speakers at a recent meeting of the Idaho State Medical Association.

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**Dr. Charles C. Gilkey,** who practiced at the Santa Fe Hospital in Topeka before opening an office at Perry, has accepted appointment as staff physician at the Osawatomie State Hospital.

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**Dr. Norvan D. Harris,** Liberal, participated in a panel discussion on family counseling, with three other speakers, at a recent meeting of the Liberal Rotary Club.

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**Dr. Varden J. Loganbill** began practice in Moundridge recently, having discontinued practice in McPherson. He and **Dr. Willard K. Kaufman** will practice together, in Moundridge and Inman.

**Dr. Clifford C. Nesselrode,** Kansas City, was honored recently, on completion of 50 years as a staff member at St. Margaret's Hospital. He was guest of honor at a testimonial dinner at the hospital.

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After having been on military duty in Atlanta for two years, **Dr. Don D. Dieter** was recently released from the service and has returned to practice in Salina.

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**Dr. William J. Madden,** Goodland, has been appointed coroner of Sherman County to replace the late **Dr. A. C. Gulick.**

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The Ball Memorial Clinic, Manhattan, announces that **Dr. Kenneth M. Boese** is now a member of its staff. Dr. Boese was graduated from the University of Kansas School of Medicine in 1956 and served his internship at Wesley Hospital, Wichita.

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**Dr. Clair C. Conard,** who has been practicing in Kansas City, has joined the staff of the Dodge City Medical Center as a specialist in internal medicine.

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The Bethel Clinic, Newton, announces that **Dr. Erwin T. Olson** has rejoined its staff after having spent a year at the University of Kansas Medical Center as a resident in pediatrics.

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The Andale community, for the first time in 19 years, will have a resident physician with the location there of **Dr. Joseph Stech,** a graduate of Creighton University Medical School, Omaha, who recently completed internship at St. Joseph Hospital, Wichita.

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The American Board of Obstetrics and Gynecology announces the certification of **Dr. Larry L. Gossack,** now practicing at Forbes Air Force Base, Topeka.

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**Dr. Nelson C. Morrow,** Parsons, has announced his retirement and plans to move to Claremont, California. He began practice in Altamont more than 50 years ago and moved to Parsons after military duty in World War I.

**Dr. Homer L. Hiebert,** Topeka, spoke to the Wyandotte County Tuberculosis and Health Association in Kansas City recently on the subject of the x-ray screening program sponsored by the state association.

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An office in Kansas City has been opened by **Dr. John E. Ingram,** a graduate of Creighton University School of Medicine who recently completed his internship at St. Margaret's Hospital in Kansas City.

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**Dr. Richard L. Dreher,** Salina, recently became a fellow of the American Academy of Pediatrics.

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The Ashley Clinic at Chanute announces that **Dr. A. A. Kihm** is now a member of its staff. He was graduated from the University of Kansas School of Medicine in 1955 and has been practicing in San Luis Obispo, California, since completing his internship.

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**Dr. Henry H. Loewen,** Wichita, who recently took a trip around the world with 16 other physicians to study medical conditions in 15 countries, told of his trip at a recent meeting of the Sedgwick County Medical Assistants Society.

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The Achenbach Memorial Hospital in Hardtner announces that **Dr. Kenneth D. Zimmerman,** who recently completed a residency in internal medicine at St. Francis Hospital, Wichita, has joined its staff.

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**Dr. Philip J. Antrim,** who has been spending three days a week in Luray, has announced plans to close his office there to devote full time to his practice in Russell.

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A tribute to **Dr. William G. Norman,** Cherryvale, was published in the July 18 issue of the *Cherryvale Republican*. Although he is 85 years of age, Dr. Norman has been caring for patients there in the absence of other physicians.

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**Dr. W. Clarke Wescoe,** dean of the University of Kansas School of Medicine, addressed the Kansas City (Missouri) Rotary Club recently on the subject of medical education and medical progress.

# Lead Poisoning

## *A Study of Such Toxicity in Children*

**CHESTER I. BARE, M.D.,** ***Kansas City***

Although the incidence of lead poisoning in children has been reduced in recent years, it is still an important problem which often goes unrecognized and can be accompanied by fatal and irreversible sequelae. It still constitutes one of the major poisoning problems[32] in children. In view of the success of present therapy, it seems worthwhile to review the literature on the subject and to stress the importance of having the entity in mind when confronted with the acutely ill, convulsing, or severely anemic patient.

Lead poisoning in children differs considerably from the disease in adults. Central nervous system involvement[38] or encephalopathy, rarely seen in adults, is common in children, whereas peripheral neuritis, lead line on gums, and colic are usually absent in children. Lead poisoning in adults is primarily an industrial problem. This paper will deal with lead poisoning in children.

### Sources

Sources of lead poisoning in children are numerous. Lead[18] may gain entrance to the body through the respiratory system by inhalation of fumes containing lead sulfide, through the gastrointestinal system by ingestion, or through the skin.

The most common source of lead intoxication in children[1, 19, 32, 36] is lead-containing paint. Frequently there is a history of the infant peeling off and eating wallpaper[1, 32] that has been painted over with lead paint or eating chips of plaster with paint on them. Fallen paint flakes also serve as a source of lead.

Today it is almost a universal practice to exclude lead-containing paint from use on children's furniture, toys, and all indoor woodwork. However, there is considerable contact, particularly in many substandard living situations, with hand-me-down repainted toys, reused nursery furniture, and repainted indoor woodwork such as window sills, which still pose a threat.

There is no legal restriction on the amount of lead[19] in paint for outdoor and indoor use. Almost all exterior house paint contains white lead in amounts up to 70 per cent, but interior wall paint, furniture paint, and enamels are usually free of lead. In many of the pale colored gloss paints and enamels used today,[21] titanium, antimony, and zinc oxides have superseded white lead. However, some yellow and green varieties still contain 20 per cent lead chromate. Terms such as "chrome-yellow," "chrome-green," or "chrome-orange" often camouflage lead chromate content in paint pigments. Unless the label excludes lead,[38] yellow, green, and orange are not recommended by the Public Health Service for refinishing children's rooms.[38] Only 19 states have labeling laws requiring that the amount of lead in the paint be specified on the can. Toys painted with coal-tar colors[19] are certified as safe by the Food and Drug Administration.

Other sources of lead are less commonly found in the home today than they were a few years ago. In 1940, after many cases of poisoning in infants were reported from the use of lead nipple shields,[19] a law was passed prohibiting the manufacture of this product. A few cases[2, 12] have been traced to ingestion of wax crayons and the inhalation of colored chalk dust with lead in the pigment. White blackboard chalk is made of gypsum and contains no lead. Some porcelain and pottery contains minute amounts of lead in the surface glaze,[19] but the only possibility of excessive ingestion of lead would be from using them as a container for lemon juice, vinegar, or other acids for several hours. Today lead toys are seldom found in the house, but they were formerly one of the major sources of lead poisoning or plumbism. Gibb and MacMahon[21] report that paint and toy soldiers account for more than half of the cases reported in Great Britain during the present century.

### References

In some condemned houses[19] in various cities, the water may be dangerous because of lead used in piping. The Public Health Service sets the safe limit of lead in drinking water at five hundredths (0.05) parts per million. The maximum daily ingestion of about five tenths (0.5) mgm. of lead in food and drink is considered safe.

A few years ago in Japan[1] infants nursing at the breast suffered what was thought to be a new kind of meningitis. Investigation disclosed that the mothers were using a lead-containing body powder on

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This is one of 11 theses, written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be the best by the faculty at the school. Dr. Bare completed his internship at St. Luke's Hospital, Kansas City, Missouri, last month and has begun a residency in pediatrics at the University of Kansas Medical Center.

their breasts which was inadvertently ingested by the infants during nursing.

The inhalation of lead vapors sufficient to cause intoxication in children has occurred frequently from the burning of discarded wooden lead battery casings for fuel in the home. There was an outbreak[18, 32] of such intoxication in Baltimore in 1932. Battery cases are impregnated with particles of lead sulfide which are vaporized when the casings are burned. The discarded cases serve as a good source of fuel for heat during times of family economic distress.

## Incidence

The true incidence of lead poisoning[23, 32, 33, 38] cannot be ascertained because lead poisoning is not a reportable disease; consequently, little statistical information has been available on mortality and almost none on morbidity. However, the condition is widespread throughout the United States and Canada, and it is now recognized as one of the major poisoning problems[32] in children. Most of the cases are reported from larger cities where children's hospitals or local health authorities are especially interested in the problem. During the period 1931-1940, the city of Baltimore[39] accounted for 49 or 24.3 per cent of the 202 deaths reported from throughout the United States. Twenty-one cases of lead poisoning[25] in Chicago in 1953 were uncovered, five of which were fatal. Over one-half of these patients were at one hospital. This high incidence in Baltimore and at the one hospital in Chicago indicates a failure to make the diagnosis elsewhere.

At Children's Hospital in Washington, D. C.,[32] from 1950 to 1954, 17 patients with plumbism were admitted, with one fatality. Lanza[23] reported in 1935 that in no year since 1920 have there been as many as 150 deaths in registration areas in the United States. A recent trend of a decrease in diagnosis[39] has been ascribed to the ban imposed on lead-containing paints for furniture and toys.

Analysis of data[38] of 347 cases of lead poisoning in Baltimore between 1931 and 1951 and other reports has brought to light interesting patterns in seasonal incidence of the disease, age and color distribution of the children, and types of houses involved.

Incidence of plumbism varies with age.[19, 25, 32] The maximum number of cases occur between one and one-half and three and one-half years of age. This corresponds to the age group where objects are put into the mouth almost as a matter of routine. This is an age period when risks of accidental poisoning from a wide variety of substances besides lead are greatest. Of 17 cases reviewed by Ryan[32] at Children's Hospital in Washington, D. C., the youngest child was 16 months and the oldest four years with a mean age of two years. The Baltimore study shows that 60 per cent of cases occurred among children in the second year of life. Only 2.3 per cent of cases were in children above five years of age.

The annual attack rate for the age segment under five years during the 1931-51 period was 7.5 times higher among the Negro population (71 per 100,000) than among the white population (9.5 per 100,000). The racial difference in incidence here is believed to be due to environmental factors, probably resulting chiefly from economic disadvantages. Other investigators[32, 38] have found no significant racial or sex predominance among the lower economic classes.

It has been pointed out[13, 25, 29, 38] that there is a seasonal incidence from June to October, with an increased incidence of encephalopathy during the spring and summer months. Of 17 cases reported by Ryan,[32] 15 occurred between June and October and all but two gave definite manifestations of encephalopathy—that is marked irritability or generalized convulsions. Rappaport[29] relates this to the intake of vitamin D and sunlight and concludes that a vitamin D producing agent, either sunlight or cod liver oil, increases the amount of lead absorbed from the gastrointestinal tract.

In a series of 30 cases of proved lead encephalopathy, 24 patients had an onset of encephalopathic symptoms between the months of May and September, and two additional patients became ill in November and December. None of these 26 patients had received cod liver oil or other vitamin D preparations. The four remaining cases occurred in the fall and winter in patients who had received adequate vitamin D dietary supplement. Blackman[13] also demonstrated the onset of symptoms of lead encephalitis in 19 out of 22 cases between May and September.

A relationship to ultraviolet light[14, 19, 32] has been suggested but not established. Porphyrins are present in increased amounts in patients with plumbism and may become powerful proteolytic enzymes after sensitization by ultraviolet light. The photosensitizing action of sunlight[29] appears to produce a slight increase in the severity of poisoning in animals excreting porphyrins in increased amounts.

Cases of lead poisoning are almost exclusively limited to blighted areas. In the Baltimore study,[38] about 90 per cent of the houses where child lead poisoning occurred were tenant-occupied. Cases were concentrated in areas of known slum status and in areas where houses were old and had many coats of paint.

## Physiology

Lead products may be inhaled, swallowed, or absorbed through the skin. In children[19] the most common route of absorption of lead is by the gastrointestinal tract. This is explained by the mannerism known as pica, the indiscriminate oral sampling of non-food substances. Pica[25] is the outstanding precursor of lead poisoning in children and, to a certain degree, is a developmental characteristic in those less than two years of age. In some children this behavioral pattern may persist until the sixth or eighth year. Many theories[15] have been formulated as to what factors predispose a child to develop an abnormal degree of pica. Some have held that abnormal pica is characteristic of mentally retarded children, while others believe that nutritional or emotional factors are its cause. During the early months of a child's life, the mother makes up so nearly his total social environment that study of the mother-child relationship may prove to be the key to understanding the psychodynamics contributing to pica.

Pica[25] may be specific or general. In a specific pica the child seeks out one special substance, such as plaster, paint, fuel oil, mud, paper, wood, or crayon. In general pica, substances are chewed and eaten without partiality. Most patients in Byers and Lord's report[15] of 20 cases with lead poisoning showed general pica. Efforts to establish primary or secondary nutritional inadequacy as a cause of pica were not successful. The pica and oral play activities exhibited by the children showed a preponderance of biting over sucking. Aggressive biting by 10 of the 15 children who survived suggests an emotional basis for pica. The behavioral and psychological picture that precedes and follows lead poisoning in children has not been as well surveyed as the physiological aspects.

If dust[2, 19] containing lead is inhaled, the insoluble lead salts are dissolved in the respiratory secretions by the formation of lead protein combinations and are subsequently absorbed into the circulation. It has been demonstrated in experimental animals[27] that finer particles of lead are assimilated most rapidly, supposedly by phagocytosis. Volatile lead products, particularly tetraethyl lead, may be absorbed directly through the skin or lungs.

The absorbed lead first enters the portal circulation, but the form and the vehicle in which it is transported have not been definitely established.[19] Whether it is carried in the diphosphate form that is soluble in plasma or in red blood cells, it is, in a large degree, deposited in the liver. Much of this lead is excreted with the bile and never reaches the systemic circulation. The remainder, regardless of the compound which was originally absorbed, enters the systemic circulation and is deposited either in the bones as an insoluble tertiary phosphate along with calcium or throughout the viscera in the soft tissues. Liver, muscle, kidney, pancreas, and spleen are the usual sites of early deposition, an exception being tetraethyl lead, which is readily soluble in fats, and concentrates[2] in the central and peripheral nervous systems. After a few days, however, most of the lead[4, 19] gradually collects in the growing ends of the long bones and in the margins of flat bones. These deposits are not generated rapidly enough during early phases of lead poisoning to show up as the typical lead line seen on x-ray.

Data[4] indicate that a small lead excretion in urine occurs daily in the vast majority of people with no unusual exposure to lead, presumably from food products. The normal urine level[32] is considered to be 0.02 to 0.08 mgm. per liter, and the normal blood level is 0.04 to 0.06 mgm. per cent.

There is a parallelism between the behavior of calcium and that of lead.[4, 27] Factors which favor deposition of calcium also favor deposition of lead, and the same applies to mobilization. Stored lead in bones produces no deleterious effects except that it may cause caries in teeth, but it may be released during subsequent illnesses and then cause symptoms of lead poisoning. Aub[4] developed the original contention that when calcium is being deposited in bones, circulating lead is also deposited in bones; and, when calcium is being pulled from bones, some stored lead is also being liberated. Sobel and Burger[34] found that when lead was fed to rats, the lead in the blood came from the diet; but, when feeding of lead was stopped, the lead in the blood came from the bones. When lead was being fed, the addition of vitamin D to the diet increased the rate at which lead was deposited in bones, and when no lead was being fed, a high-calcium, low phosphorus diet caused the most rapid loss of lead from the bone.

Bone trabeculae, particularly at the epiphysis, act to readily supply calcium for the body needs. The trabecular structure is depleted when calcium is demanded by the body and refilled when calcium is stored. Lead is stored in trabeculae in relatively high concentration. Probably not all of the calcium and lead that is liberated from bone is excreted. X-ray evidence indicates that it may circulate and be redeposited in bone, especially in childhood, for roentgenograms show that lead gets repeatedly dissolved and redeposited along epiphyseal lines of growth.

The circulating blood level,[19, 32] the rate of deposition of lead into the tissues and bones of the body, and its ultimate excretion are altered by conditions such as diet, infection, and acidosis. If the diet contains an adequate amount of milk, lead will tend to be deposited more rapidly in the ends of the long bones. If the diet is deficient in milk, or if there is an intercurrent infection with acidosis, lead is more rapidly withdrawn from bones and tissues into the circulation. Once the source of lead is removed, lead in bones and tissues is gradually excreted from the body by normal physiological processes. The amount of lead in the urine roughly parallels the amount of lead in the blood and thus serves as an indication of the rate of transport of lead.

## Symptoms, Diagnosis, and Pathogenesis

Lead poisoning[18, 23] is prevalent though many cases are mild. Both mild and severe cases are commonly not recognized. The occurrence of symptoms depends upon the amount of lead in the soft tissues. The human body[27] can accommodate large quantities of lead, when gradually absorbed, without producing symptoms, and it is clinically important only as it may be a forerunner of lead poisoning. When absorbed lead causes symptoms it is assumed that organ damage has occurred.

Lead poisoning may be either acute or chronic. Acute lead poisoning in children[18, 19] is rare. When it does occur, it is caused by a sudden, overwhelming exposure to lead such as in the inhalation of fumes from the burning of storage battery casings or the accidental ingestion of lead salts. The onset of symptoms is abrupt, with nausea, vomiting, and abdominal pain. This may be rapidly followed by muscular weakness, pain, or paralysis. Hemolytic crisis[17] may occur, and death is not uncommon within a few days.

Chronic lead poisoning[19] is more common in children because they are more inclined to ingest small amounts of lead over a long period of time. Symptoms do not depend on the amount of lead absorbed at one time, but upon the amount absorbed over a given period of time and its subsequent release from soft tissues or bones. Therefore, symptoms are commonly intermittent, with exacerbations being stimulated by such factors as infections or metabolic disorders, which mobilize lead that had previously been deposited in bones and tissues. The history is frequently that of periods of well-being interrupted by periods suggestive of poisoning.

The onset of symptoms[18, 19, 32, 36] is frequently insidious and may be mild in infants. One of the earliest symptoms is a change in disposition. The child may become restless at night and peevish during waking hours. Constipation, alone, may be present for months, but occasionally diarrhea is a presenting symptom. Gradually increasing anorexia, loss of weight, pallor, irritability, and then abdominal colic and vomiting are frequently presenting symptoms. Abdominal pain is often accompanied by abdominal distention. Aub[4] has stated that the colic is due to increased tonicity of the smooth muscle of the intestine and that lead works directly on this smooth muscle, possibly in addition to effects on the sympathetic nervous system. A spontaneous disappearance of colic and vomiting may lull the physician into a false sense of security. In lead colic[18] and spastic constipation there is a tendency for involvement of the vascular system of the upper portion of the digestive tract which may lead to gastric ulcer formation.

The most prominent and severe symptoms of chronic lead intoxication in children are those referable to the central nervous system. Evidence of encephalopathy may not appear until the disease has existed for a long time, or it may appear suddenly in association with some secondary disturbance producing a rapid release of large amounts of stored lead. The onset of encephalopathic symptoms is relatively abrupt, with severe and repeated convulsions. The convulsions are usually generalized but may be focal, and sometimes focal attacks occur on both sides of the body in irregular sequence. Sometimes the convulsions are difficult to control, and children often die in a series of violent attacks. In the interval between convulsions, the child may be drowsy or even comatose, but states of excitement and delirium are also seen.

In 22 cases of encephalopathy due to lead, Blackman[13] reports that the onset of vomiting in ten cases occurred within three weeks prior to the first convulsion. In many cases convulsions were preceded by behavior changes such as nervousness, irritability, listlessness, disobedience, and crying spells. Transient cerebral palsies are not uncommon between convulsive episodes. Involvement[25, 32] of the central nervous system is manifest not only by irritability and convulsions, but also by disorientation, hemiparesis, general flaccidity, ataxia, retrobulbar neuritis, optic atrophy, hyper-reflexia, gross tremors, and pathological reflexes such as Kernig's and Babinski's. In severe cases[1] there may be separation of the suture lines of the skull and hypertension. The temperature is usually normal but may be slightly elevated.

Polyneuritis, though much less common than encephalopathy, may occur, especially in older children. In contrast[29] to wrist drop and foot drop seen in

adults, paralysis is not so selective in children and involves all the muscle groups, flexors and extensors.

The lower extremities[26] are usually more severely affected than the upper extremities, and distal muscles are involved more frequently than proximal ones. The gait[18] has been described as characteristic in that it is a waddling type in which the child walks on the outside of his feet, drags his toes, and with each step swings his legs sideways before putting his feet to the ground. Muscle cramps, especially in the legs, are common. Joint pains and soft tissue swelling of the hands, feet, and face often occur. No morphological damage[27] in the joints has been found to explain joint pain. Stored lead in the bones does not cause these or other symptoms.

The single factor most important in making the correct diagnosis in lead poisoning is proper history taking. A history[1] of lead ingestion is generally difficult to obtain and often requires direct questioning; even then the parent's replies may be vague and misleading. With a high index of suspicion, vomiting, abdominal pain, and constipation or diarrhea should be sufficient reason to question the mother[17, 18] for the presence of pica and to look for positive findings.

Diagnosis[12, 25] of lead poisoning in children can be difficult since the onset may be insidious and early symptoms—restlessness, easy excitability, pallor of skin, anorexia, constipation, headache, colic—may resemble those of many other diseases. Physical examination,[32] in general, is not contributory except when manifestations of central nervous system involvement are present. Lead poisoning should always be considered in a differential diagnosis of convulsions.

The abdominal symptoms[19] of lead poisoning have resulted in erroneous diagnoses varying from epidemic vomiting to mesenteric thrombosis. Frequently, patients have had an appendectomy with temporary relief of symptoms. Acute intestinal obstruction, intussusception, and Meckel's diverticulum may mimic lead colic, with constipation, vomiting, blood in the stools, and rhythmical abdominal pain. Other diagnoses[9, 19, 23] have included perforated peptic ulcer, gallbladder disease, and pancreatitis. Muscle pain has resulted in a primary diagnosis of osteomyelitis and tuberculosis of the hip.

Encephalitic symptoms, common in children with plumbism, often result in the diagnosis of tuberculous meningitis. This is a natural mistake to make according to Ford,[20] especially if the tuberculin test is positive in a young child with stupor, rigidity, and increased protein and cells in his spinal fluid. Often cases are misdiagnosed as behavioral problems, expanding cranial lesion, or epilepsy. The polyneuritis of lead poisoning has been confused with poliomyelitis, Guillain-Barré syndrome and spinal cord lesions. If several cases occur within a short time, an epidemic of viral encephalitis may be suspected.

The best laboratory evidence[19, 32] of lead poisoning consists in demonstration of excess amounts of lead in the blood and urine. The technique for analysis of lead is difficult and time consuming. The amount of lead in the urine parallels the amount of lead in transit within the body.

The hematopoietic system[1, 19, 27] is significantly altered by lead exposure. Red blood cells exhibit two changes with sufficient frequency to be useful, though not definitive, diagnostic aids. These are hypochromic anemia and basophilic stippling. The effect of lead[18] on bone marrow may be so irritating as to result in a decreased output of normal blood cells—by release of immature red blood cells and producing a relative increase in the number of mononuclear leukocytes. The total white cell count, however, is usually normal. The basophilic stippling of red blood cells is generally considered as an important sign of lead absorption. This stippling may vary considerably in size from minute stippling to large aggregates of basophilic staining material within the cell. Stippled cells may make up as much as four per cent or more of the red blood cells. Such cells, however, may be found in infectious diseases, blood dyscrasias, advanced malignancies, and poisoning from other causes; but in no other disease are stippled cells so profuse in the absence of other major blood changes.

Usually stippled cells disappear from the blood two to four weeks after cessation of exposure to lead. Stippling has never been fully explained, but it has been considered to be degenerated reticulocytes, juvenile red blood cells, or manifestations of polychromatophilia. In a review[32] of 61 cases of lead poisoning in four different series, stippling occurred in from 53 to 81 per cent. Stippling[1] is apparently an index of the stimulation of erythropoietic activity of bone marrow.

Lead causes an increased hemolysis of red blood cells. In 18 cases out of 21 reviewed by Mellins and Jenkins,[25] the hemoglobin level was found to be less than 10 grams per 100 cc. of blood. Hemolysis due to increased erythrocyte mechanical fragility has been suggested[37] as one of the mechanisms of anemia. Aub and co-workers[5] found evidence of hemolysis in four patients, as indicated by elevation of the indirect serum bilirubin. Hemolysis in these patients was found not to be due to increased erythrocyte osmotic fragility, for the red blood cells were resistant to hemolysis in low salt concentrations.

Morgan[27] states that lead interferes with the synthesis of hemoglobin, lowering the hemoglobin level and causing an organic pigment normally contained in the heme component of hemoglobin to be excreted as coproporphyrin in large amounts in the urine. The urinary porphyrin test is usually an earlier guide to lead damage than is the stipple count.

Less frequent and more controversial are the effects of lead on the vascular tree of adults,[27] particularly its association with hypertension. There is no doubt that in adults hypertension occurs frequently in association with lead colic, but this may be purely a reaction to pain. Cerebral manifestations may mimic hypertensive encephalopathy clinically, and the frequent occurrence of hypertension with the presenting picture has been thought to indicate hypertension secondary to lead as the causative factor. However, in studies of patients exposed to lead[27] for many years, there is no convincing evidence that hypertension is more frequent than would be expected in an unexposed group.

Just as increased stippling is not specific for lead poisoning, neither is an increase in the urinary porphyrin level.[18, 27] Some of the causes of porphyrinuria are infectious diseases, liver diseases, blood dyscrasias, deficiency diseases, skin diseases, and drugs; however, an increase of urinary porphyrin[27] due to stimuli other than lead poisoning is small. Normal urine, for instance, contains 10 to 30 micrograms of porphyrin per liter; in benzene poisoning this level may be 255, while in lead poisoning it is over 3,500 micrograms per liter. It is not uncommon for the urine to contain increased amounts of albumin, acetone, and granular casts.[18] Occasionally sugar will be present. Glycosuria[19, 39] is thought to be of renal origin and is not accompanied by hyperglycemia or polyuria.

Damage to the renal tubules[25, 27] may occur in massive lead poisoning, the changes being similar to those produced by other heavy metals. It is thought that repeated episodes of poisoning over a long period cause nephrosclerosis as a component of generalized vascular damage. Oliguria, hematuria, and albuminuria may be noted coincident with the appearance of symptoms of lead poisoning, and these urinary findings usually clear as the symptoms are relieved. Fatty vacuolation and intranuclear inclusion occur in the cortical tubules.[36, 39]

X-ray studies[1, 18] of growing bones in chronic lead poisoning reveal a deposit of tertiary lead phosphates in the ends of the shaft of long bones and along growing margins of flat bones. These are similar roentgenographically to the so-called growth lines except that lead lines are usually heavier and thicker. Since these lines are not generated rapidly, they are usually of no value in studying the early case. In the chronic form of plumbism they are almost a constant finding except when active rickets is present. Occasionally opaque lead-containing material is visible in the intestinal tract on a flat plate of the abdomen. Roentgenographic changes show a variable degree of persistence. In 26 patients in one series,[36] complete disappearance of the lead line at the distal end of the shaft was eventually noted with recurrences six to seven months later in two patients who had reinstituted the paint chewing habit.

During acute infections and metabolic disturbances lead may disappear from the bones[19] and reappear in the circulation. Thus lead poisoning, with all its clinical and laboratory manifestations, may exist in the absence of a lead line in bones. This line[26] of increased density, by itself, does not incriminate lead as similar findings are sometimes seen in normal patients as well as in those with healing rickets, other metabolic diseases, and poisoning with other heavy metals such as phosphorus, bismuth, and titanium.

Spinal fluid may be normal, especially in those cases without encephalopathic symptoms; however, it may be under increased pressure, with greatly increased protein, a positive globulin reaction, and changes in the cell count from normal to 100 or more lymphocytes, the average being 30 to 40 cells.

Severe lead poisoning often occurs with the absence of a lead line in the gums of children. Ryan[32] states that the lead line occurs in less than two per cent of children with lead poisoning. It is never present in infants[18, 19] without teeth. When present it is frequently seen on the buccal rather than labial aspects of the gums, and often near the molar, rather than the incisor teeth. Lead[27] combines with decomposed food and gum tissue to form a number of minute granules of lead sulfide in the gums. It may exist as a group of discrete brownish dots, rather than as a line. Poor dental hygiene[8] is necessary for its formation, and even with severe lead poisoning the lead line may be minimal if the gums are scrupulously clean.

In acute lead encephalitis,[18, 27] the brain is swollen with flattening of the convolutions and may be hyperemic or pale. Vascular lesions including capillary necrosis and thrombi are sometimes seen. Hemorrhage and round cell infiltration within the pia and an increase in neurologia cells of the cortex may be present. Most of the injury to nervous tissue[13] seems dependent on an accumulation of exudate, a serous fluid usually without fibrin. Lesions are patchy in distribution and are found throughout the entire central nervous system, being most abundant in the

cerebral hemispheres and cerebellum. In peripheral nerves the axon and whole cell may be destroyed.

The direct effect of lead on the smooth muscle[27] of the intestinal tract is thought to explain the constriction of the small intestine and the resultant colicky pain. X-ray studies during colic do show hypermotility and spasm of the small intestine with subsequent atonicity as the pain eases.

Lead palsy or the muscle weakness seen in lead poisoning[27] is due to a direct effect of lead on the voluntary muscles. Lead interferes with the resynthesis of phosphocreatine. Because this chemical effect hinders the recovery of muscles following use, the most exercised muscles are involved. In children this is usually dorsal flexion of the foot in contrast to the wrist drop seen in adults. Degeneration of the anterior horn cells[24,25] has been noted at autopsy, and this may explain the muscle atrophy occasionally seen in lead poisoning.

### Sequelae and Prognosis

The sequelae of lead intoxication in children appear to be mainly neurological. Little interference in physical development has been reported. However, residual effects of toxicity on the central nervous system[18] are at times permanent and progressive. Encephalopathy is common in young children, and the prognosis is serious with a mortality of 20 to 30 per cent in some series.[1] Mentality frequently remains impaired with a tendency to mental sluggishness and melancholia if the patient survives.

In one series[32] of 59 cases there were 17 deaths or a 29 per cent mortality. In another series[12] of 20 cases admitted with convulsions there were 13 deaths or a 65 per cent mortality. Of 26 children treated by Thurston and associates[36] from 1940 through 1949, seven or 27 per cent died. Cotter[16] states that in the United States some thousands of cases of lead encephalopathy occur annually in children up to three years of age and that the mortality in this group, so far as is recorded, exceeds 25 per cent.

Byers and Lord[15] note in a study of 20 children who had lead poisoning in early infancy that, despite normal motor development during infancy, only one child lived up to the promise of his early development. In a few children successive psychological examinations showed significant drops in intelligence quotients. This was thought to be a result of failure of mental development rather than actual mental deterioration. In other children the intelligence quotient remained well within normal limits. Along with a dilatory effect on mental growth, an increased percentage of behavior difficulties was found.

All 20 patients of Byers and Lord regressed emotionally and behaviorally during and immediately after the severe illness. This, in itself, is not unusual, but the failure to catch-up during the period of convalescence would seem to indicate that lead poisoning caused retardation beyond that which commonly accompanies a serious illness and hospitalization. Approximately six months after recovery from the acute episode, 14 of the 15 surviving children were found to be retarded in some way. Language ability and finer muscle coordination were most disturbed. Extreme distractibility, short attention span, and a high variability on psychological tests were characteristic.

Thurston and co-workers[36] found no evidence of mental deterioration in their series of 11 cases. Two of the 11 children later had bilateral optic atrophy, and a third child had a high degree of myopia. They felt these children were at a serious disadvantage because of the mode of instruction in primary grades and should receive special attention to offset visual-motor deficits. No direct correlation between the severity of the illness and the amount of residual effect was noted.

### Treatment

The problem of treating lead poisoning is in controlling the deposit and excretion of lead from the skeletal storehouse.[4] A new compound for treatment of lead poisoning has been available the past four years since development of the neutral disodium calcium salt of ethylene diamine tetraacetic acid (EDTA).

Earlier treatment regimens[32] consisted of first inducing the deposition of lead in the bones and tissues by a high calcium diet and adequate vitamin D to reduce toxic blood levels, and then instituting carefully controlled deleading processes once the acute phase had terminated. Previous methods[11] of deleading which were most successful were the use of citrate, phosphate and 2, 3, dimercapto-n-propanol (BAL). However, complexes formed by lead with these substances do not remain sufficiently stable to prevent the toxic effect of free lead during excretion via the urinary bladder or gut. The danger of causing encephalopathic symptoms during any deleading process is always present. Sodium citrate forms lead acetate, which is metabolized in the normal oxidative process, thereby freeing lead to form complexes in soft tissue.

BAL competes with the sulfhydryl containing enzymes for heavy metal. It has been demonstrated that lead may completely inactivate the sulfhydryl-containing enzyme, succinoxidase, and that reactivation occurs with the addition of BAL.[7] The results of experiments with rabbits, however, suggest that the lead-BAL complex is more toxic than lead alone.[1,33] Clinical results have been controversial. BAL has far

less affinity for lead and causes less enhancement of excretion of lead than CaEDTA.

EDTA belongs to a class of compounds known as chelates, a word derived from the Greek for claw. All chelating agents possess two or more active groups, which are capable of forming bonds with multivalent metals. When chelation involves a multivalent positive ion[31]—for example, calcium—the calcium ion becomes an integral part of the ring structure and in so doing the calcium ion loses its ionic properties. Frequently chelating agents will form a water soluble product with a multivalent positive ion. This is true of CaEDTA,[37] which forms a stable, water-soluble, non-ionizable ring complex with a variety of metallic ions.

The special property of EDTA which makes this compound particularly active in bonding to heavy metals is due to two nitrogen atoms in the molecule which forms additional bonds. Thus at physiologic pH, each heavy metal ion is bound to a single molecule of EDTA by four bonds.

Although EDTA can form a complex with almost any metal,[11,33,37] the strength or stability of the complex with different metals varies, and a metal which forms a stronger complex can replace one which forms a weaker complex. The alkali metals, Na and K, are held most weakly; the alkali earths, Ca and Mg, and the rare earths and di- and trivalent cations, Pb, Cu, and Ni, follow in increasing degree of chelate stability.

EDTA[11] forms such a tight complex even with calcium that it can be used as a laboratory anticoagulant. It can combine with serum calcium to the extent of causing hypocalcemic tetany and eventual death in hypotension.[28] Since this calcium complex is nontoxic on slow intravenous administration,[35] and since lead will replace the calcium of the complex, CaEDTA is theoretically the method of choice for administration of EDTA in lead poisoning. It has been shown[35] that parenteral CaEDTA causes no appreciable decalcification and that it results in the increased urinary excretion of lead in experimentally poisoned animals.[3]

As one would expect in view of chelation preference, when unbound EDTA is administered rapidly to animals and humans, the serum calcium decreases and tetany may ensue.[28] When administered as the preformed calcium chelate (CaEDTA), however, serum calcium levels remain unchanged.[37] The calcium ion of CaEDTA is readily replaced by cobalt, zinc, lead, copper, and nickel because of the greater stability constants of these heavy metal chelates. The copper and nickel ions are only slightly stronger than lead in their degree of chelating stability.

Once lead is bound to EDTA,[11] it has a different distribution than the free metal, for its passes freely through most of the body membranes and is excreted rapidly by the kidney. Ninety-five[33] to 98 per cent of $C^{14}$ labeled CaEDTA, administered parenterally to rats, was recovered in the urine within six hours. The urine output[30] was found to be increased in all patients while the drug was being administered. This increase in urine volume was greater than could be accounted for by the volume of the five per cent glucose solution in which the drug was administered, or by an increase in oral fluid intake.

Two mechanisms may be operating in effecting some measure of diuresis. It has been found in studies conducted in vitro[30] that CaEDTA removes lead from kidney slices more rapidly than from slices of other tissues. The kidney may, therefore, be one of the first organs whose lead load is lightened sufficiently to show considerable improvement in function. This observation is borne out by the fact that five of nine patients showed some objective signs of impaired kidney function before therapy, and these signs were absent following treatment. However, all these patients showed a 10- to 40-fold increase in urinary excretion of zinc.[30] This observation raises the possibility that the drug takes zinc away from carbonic anhydrase, thereby inhibiting this enzyme and causing diuresis.

The lead complex[11] itself is relatively non-toxic, and no symptoms of lead poisoning are shown by animals receiving amounts of lead-EDTA, which as a free metal would cause fatal intoxication. The same phenomenon appears in patients with lead encephalopathy who receive CaEDTA. Calcium is exchanged for lead, and the blood level of lead rises to heights never before found in surviving patients; yet even at the height of the blood lead level, the patient is improving.

It has been demonstrated[33] that CaEDTA does not enter the red cells, is not metabolized, does not concentrate in any organ or tissue, is excreted by the kidney in a manner similar to Diodrast, and rapidly leaves the vascular system to mix with approximately 90 per cent of the body water. Metabolic inertness and rapid and complete excretion account in part for the low toxicity in animals and the absence of toxicity in humans when recommended dosages are used.

In children,[33] the blood lead level rises noticeably during therapy without exacerbation of symptoms. Adults receiving intravenous treatment consistently show a fall in blood lead values during treatment, but with a rebound in the first weeks following treatment. The value subsequently falls. This rebound phenomenon has not been associated with a recurrence of symptoms. Rebound is not seen in patients

during the course of therapy. This difference of response of blood lead concentration in children and adults may be due to the more rapid metabolic turnover in children, hence the stored lead is mobilized with greater facility. In adults the lead is apparently chelated and the complex excreted more rapidly than lead is mobilized, resulting in a fall of blood lead concentration during therapy.

CaEDTA removes lead in vivo only from soft tissue,[30] and following deleading of soft tissue normal metabolic turnover of bone tissue results in a renewed build up of lead levels in soft tissues. This constitutes a potential source of lead poisoning for some time following a course of therapy with CaEDTA. Some time after an infusion of the drug, if it is again given, the lead which will have accumulated in soft tissues can again be removed with considerable efficiency.

No toxic effects[17,37] from CaEDTA have been reported. However, it has not been conclusively demonstrated that EDTA will not inactivate trace metal containing enzyme systems necessary to normal metabolism. Only about one per cent of the CaEDTA[16,22] administered is recovered as lead-EDTA, which further suggests a possible formation with trace metal complexes.

The rapid and marked decrease of urinary coproporphyrin excretion[30] indicates that toxic effects of lead on erythrocytic cells are arrested almost as soon as therapy with CaEDTA is initiated.

In treatment of lead poisoning Belknap and Perry[10] have found, regardless of the amount of lead in the system, that excretion of lead reaches a peak in 24 to 48 hours after treatment with CaEDTA is started. For this reason they advise giving the compound for two days and omitting it for five days and repeating this cycle until the pathological deposits have been removed.

The drug may be administered intravenously, subcutaneously, or orally. Parenterally[33] the drug is usually diluted in order to avoid any possibility of phlebitis. Intramuscular injections, even when one per cent procaine is added, have been painful to some patients; hence they are not used.

The problem of an optimal dose is a difficult one and has not been fully agreed upon. For oral dosage, Sidburg[33] recommends 30 mgm. per kgm. of body weight for both children and adults given before breakfast and supper with liberal amounts of water. A larger oral dose resulted in diarrhea and abdominal pain.

Sidbury[33] recommends as an intravenous dosage for adults one gram on the first day and two grams a day thereafter for a total of five days. He gave the drug in divided doses twice daily in 250 cc. of five per cent glucose in water by slow infusion. No significant toxic effects were encountered from this dosage in over 35 patients—even though about 30 per cent had evidence of renal pathology.

Bessman and associates[11] found that doubling the amount of CaEDTA caused about the same excretion as an initial dose of 0.5 grams. This suggests that either the available lead had been used up or that in doses greater than 0.5 grams the CaEDTA is excreted too rapidly to permit it to come into equilibrium with body fluids. Bessman and associates[11] used 0.5 grams of CaEDTA subcutaneously or intravenously every eight hours for five days, followed by a three-day rest period with repetition of a five-day course. In treatment of seven cases of lead encephalopathy they noted no signs of toxicity from CaEDTA. The final dosage and schedule of administration of this drug await further experience by these workers.

With a rest period[18] interposed between therapy there is a lessened likelihood of depleting essential trace metals by chelating with EDTA and excretion along with lead.

In addition[32] to this specific method of treatment there remain the usual supportive measures. Sedation, analeptic medication, blood transfusions, and even cranial decompression are frequently indicated. Convulsions can be managed by 0.2 to 0.4 cc. per kilogram of body weight of a 25 per cent solution of magnesium sulfate given intramuscularly every six hours. A rapid subsidence of lead colic occurs with slow intravenous injection of 10 cc. of a 20 per cent solution of calcium gluconate.

CaEDTA has received much acclaim as the answer to the treatment of lead poisoning. However, it has been used for a relatively short period of time, and then only in limited dosage for treatment of clinical symptoms. That it can be used as an industrial prophylactic drug seems improbable in view of evidence that chelation of trace minerals may interfere with enzyme systems of the body. Only careful and thorough investigation of this and other problems that arise can determine whether certain beneficial effects will outweigh detrimental actions which may arise from its use.

## Summary

1. Although lead poisoning is much less frequent than many other diseases in children, it is still prevalent, especially among children living in a poor economic environment.

2. Chewing on furniture, toys, or woodwork painted with lead-containing paint is the most common source of this poison.

3. A parallelism between the physiologic behavior of calcium and lead exists in the body. Some of the

ingested lead reaches the circulation and is then carried to many parts of the body, where deposition in soft tissues causes symptoms.

4. The symptoms are often insidious in onset. The diagnosis is dependent upon a history of pica, suggestive symptoms, the results of quantitative blood and urine studies, and x-ray examination of the long bones.

5. The prognosis is serious, since there is a mortality of 20 to 30 per cent in some series of cases. Sequelae frequently consist of blindness and permanent brain damage.

6. Treatment consists of specific and supportive measures. Acute cases of chronic lead poisoning have been treated with CaEDTA, which deleads the body without development of the toxic symptoms inherent in the process. Other possible toxic manifestations of this drug need further investigation before final evaluation is made.

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## Film Describes Role of Radiologist

A new color motion picture dedicated to the radiologist has been added to A.M.A.'s film library. "First a Physician" tells the dramatic story of what a radiologist is, what he does and how he serves patients. The film was produced by E. I. du Pont de Nemours and Co., Inc. in cooperation with the American College of Radiology.

Medical societies may arrange for bookings through the film library. The film will be particularly suitable for school, club, and other public gatherings.

# BOOK REVIEWS

*Hutchinson's Clinical Methods. Thirteenth Edition. By Donald Hunter, M.D., and R. R. Bomford, M.D. Published by J. B. Lippincott Company, Philadelphia. 452 pages. Price $6.00.*

The English seem to have a faculty for clear and concise exposition, and the current edition of *Hutchinson's Clinical Methods* is a case in point. It is not presented as a comprehensive treatise on diagnosis, but rather as a summary of those methods of clinical investigation necessary to the establishment of a correct diagnosis.

This book is small in size, and it is well organized so as to be a handy and ready reference for students and practitioners. It contains a great deal of material that should be of help in the clinical evaluation of a patient and the establishment of a correct diagnosis.

It is not being unduly critical to point out that coverage is sketchy in places; for example, no cold pressor test is mentioned in the section on hypertension, and no classification of eye grounds in hypertensive or arteriosclerotic disease is included.

The book is well printed on good quality paper, and the binding is quite good. A fair number of good black and white photographs, diagrams, and tables supplement the text and add to its value. As usual, color plates consist of reproductions of colored drawings rather than the more desirable color photographs and photomicrographs.

Medical students should find, in this little volume, an excellent supplement to the standard textbooks on physical diagnosis and clinical pathology; and many practitioners will undoubtedly find it to be a convenient source of reference, and, more important, a good review of things once known but now forgotten.—*J.D.R.*

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*Rypins' Medical Licensure Examinations. Eighth Edition. Edited by Walter L. Bierring, M.D. Published by J. B. Lippincott Company, Philadelphia. 964 pages. Price $10.*

Licensing boards perform a function required by the law of the states. Examinations prepared by such boards, made up of men in active practice, serve as a valuable check upon the work of medical schools. By the same token, licensing boards should be clearly aware of the progress being made in medical schools.

Every candidate for a medical license has some apprehension concerning his ability to cope with the point of view that will be taken by the state examiners concerning the answers he may give to their questions.

After a critical survey of many thousands of questions used throughout the United States, the author made a selection of typical questions which served as a basis for a most comprehensive review in major medical subjects.

With the able assistance of eminent authorities in each of the ten subjects reviewed and a study of the National Board of Medical Examiners' objective multiple choice type of examination, Doctor Bierring has re-edited this eighth edition with a view toward giving the candidate for license a comprehensive review and an assurance of a general agreement among examiners regarding essential material.—*O.W.D.*

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*Practitioners' Conferences. Held at New York Hospital-Cornell Medical Center. Volume 6. Edited by Claude E. Forkner, M.D. Published by Appleton-Century-Crofts, Inc., New York. 378 pages. Price $6.75.*

The reviewer has become familiar with and used all previous volumes of the *Practitioners' Conferences,* but finds this the most informative of the group.

Reproductions of unrehearsed, spontaneous, clinical discussion often are characterized by discontinuity, disagreement, and indecisiveness. Little of such is apparent here; and any similar weakness is more than compensated for by the complete and lucid outlines summarizing each presentation. Dr. Forkner not only guides the discussion well but adds fine editorial workmanship in the summaries. Of unusual appeal to practitioners should be the overall atmosphere of clinical medicine evident in each conference. While basic science workers contribute, the bulk of comments are not only directed at clinicians but made by practicing physicians.

Volume Six treats a total of 15 subjects including: Should Patients Be Told the Truth About Serious Illness; Trichinosis; Cancer of the Thyroid; Portal Hypertension; Early Detection of Heart Disease; Dermaphytosis; Tinea Capitis, and Monilia Infections of the Skin; Endometriosis; Gout; and other equally important areas of almost daily interest to the practicing physician. The conference on trichinosis is alone worth the price of the volume. The same could be said of the discussions of gout and cancer of the thyroid.—*M.H.D.*

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*Signs and Symptoms. Third Edition. Edited by Cyril M. MacBryde. Published by J. B. Lippincott Company, Philadelphia. 973 pages. Price $12.00.*

This book is presented as an approach to diagnosis of disease, or, to use the author's phrase "applied

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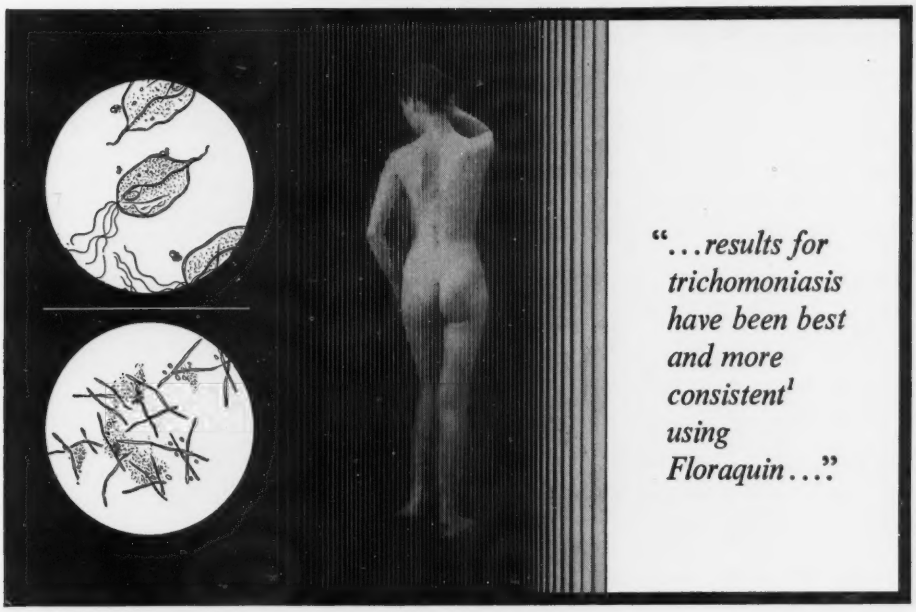


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SEARLE

pathologic physiology in clinical interpretation." As such, it deals directly with presenting complaints. It attempts to identify and differentiate possible causes and to explain the underlying mechanisms of commonly occurring symptoms. Some 28 authors have contributed portions of the text, generally treatises on a subject within their special field, and most of them are recognized authorities. The material is presented in 34 chapters, including an introductory analysis of the approach to diagnostic medicine, discussion of growth and sexual development, a series of chapters on pain in various parts of the body, chapters on specific symptoms of the cardiorespiratory system, the gastrointestinal system, hemopoietic and lymph systems, discussion of fever, a section on nervousness and neurologic disturbances, discussions of water, electrolyte, and caloric balance, and finally two chapters on the skin, all based on signs and symptoms.

This volume is not to be considered as a ready reference book or a "do-it-yourself" effort. It contains few, if any, outlines or tables, and it does not provide any mechanical magic with which to reach a diagnosis. The bulk of the material is devoted to the background of manifestations of disease and the physiologic mechanism of various symptoms and signs. It, therefore, provides a frame of reference within which an individual's complaints can be evaluated, and at the same time it attempts to cover, at least by name, all of the possible causes of any given manifestation of disease. It will be found principally useful to the physician who has read it through thoroughly and from it gained added insight and understanding of the complaints he hears each day. Once acquainted with its contents, the physician will note many clues which he might otherwise overlook, and may in addition find the volume helpful in checking on this or that question raised by some particular patient.

With this understanding of the aims of the editor, one can certainly say that this is a commendable effort, and the book is well worth reading by any physician who deals regularly with diagnostic problems. Certainly there is a wealth of material for the medical student or intern to absorb. This is a fascinating field; the more it is considered, the more could be said on the subject. Thus when one is finished reading this book, he has the feeling this is not the last word, even though there is no other volume available approaching the subject in exactly the same way.

It is obvious that the editor has had to make many compromises in balancing the content and emphasis. Some relatively minor subjects receive a considerable amount of space (such as fainting, not including convulsive seizures, with 14 pages, or headaches with 43 pages) while others are skipped through rather superficially (such as the chapter on nervousness and fatigue, which also includes only 14 pages). Obviously, attention must be given to exotic and rare conditions which may present a given sign or symptom, but at the same time a practical diagnostic approach gives first emphasis to common causes. Throughout the volume mention of psychogenic factors is made regularly, and yet in only a few cases is this aspect adequately discussed. Possibly a companion volume devoted principally to this subject, and to the important question "Why does a given patient come to a physician at any given time?" would serve to balance the more technical material.

So far as the details of publication are concerned, they are generally satisfactory. The printing and format are good. There are not many illustrations for a book of this type, yet some are not too important. In particular, of the six color plates, only two seemed really necessary and useful, whereas numerous opportunities for others are overlooked. In a few places, proprietary names of drugs are used in a rather careless fashion. Adequate bibliographical material is presented at the end of each chapter, and there is a useful index.

This is a worthwhile book, and one which has obviously improved and rounded out as it has gone through the editings. Possibly the material could be handled in fewer pages, but it will prove interesting and instructive to the physician who is really interested in the art and science of diagnosis, and as such it can be recommended.—*J.E.S.*

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*Gifford's Textbook of Ophthalmology. By Francis Reed Adler, M.D. Published by W. B. Saunders Company, Philadelphia. 499 pages. Price $8.00.*

The original *Textbook of Ophthalmology* by Dr. Gifford is familiar to many of us because it has been the standard book used in many medical schools and also by many general practitioners as a ready reference book.

This edition covers the subject of ophthalmology very well. It has many additions such as the treatment of diseases with the new drugs. The portions dealing with tuberculous and syphilitic diseases have been deemphasized, and rightly so, since they are far less common today.

It is true that there have been volumes written and published on any one of the subjects covered in these chapters; however, many of these conditions are of interest only to the ophthalmologist. The cov-

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erage in this book is adequate for the medical student or the general practitioner.

With advances that have been made in color photography, it would seem to me that more color plates of such things as arteriosclerotic and diabetic retinopathy, conjunctival lesions, and optic nerve disease would be of great value from a teaching standpoint.

I would recommend this volume to any teaching institution or practicing physician for a reference book.—*R.R.P.*

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*A Manual of Pharmacology. Eighth Edition. By Torald Sollmann, M.D. Published by W. B. Saunders Company, Philadelphia. 1535 pages. Price $20.*

Probably every practicing physician over the age of 40 cut his pharmacological eyeteeth on Sollmann's *Manual of Pharmacology,* as this book had the field pretty much to itself until about 15 years ago. Everyone realized that, as a textbook, it left a great deal to be desired, but in spite of its rather haphazard organization it was the one book upon which one could depend for needed pharmacological information almost every time. Where else can one find reassurance for the frantic mother whose little darling has just eaten a handful of bittersweet berries?

To quote from the author's preface: "The purpose of this Manual is to furnish a guide through the complexities of modern pharmacology—the actions and uses of drugs. Contributions to this subject are being published at an ever-accelerating rate and the wealth of material is indeed confusing. The Manual aims to summarize critically the chief features of these contributions."

Dr. Sollmann has fulfilled his aim admirably in the past, but it is a disappointment to have to report that the present edition shows signs of haste and careless editing. Even as erudite and accomplished a pharmacologist as the author seems to have been confused by the "ever accelerating rate" of contributions to the pharmacological literature. Therefore, one cannot depend upon the book for authoritative statements about new drugs. This is especially unfortunate as students and physicians have the utmost difficulty in locating precisely this type of information.

As a case in point, "Frenquel" and "Meratran" are discussed as trade names for pipradrol hydrochloride. Actually "Frenquel" is the trade name for azacyclonol, and the two drugs, even though they are isomers, have entirely different pharmacological actions. Furthermore, "Meratran" is misspelled, "Meradran," which cannot fail to add to the confusion. Furthermore, meprobamate ("Miltown; Equanil") is misspelled both in the text and in the index, and the section on this widely used drug is wholly inadequate.

The chapter on adrenal cortical hormones contains a great deal of interesting and important information, but it lacks the organization which could unify and simplify the subject, and it does not contain the graphic formulae which are so important in delineating the structure-action relationships. Incidentally, fludrocortisone is misspelled.

The oral hypoglycemic agents, carbutamide and tolbutamide ("Orinase") are given sketchy treatment at the end of the chapter on sulfonamides. One could also go into the shortcomings of the section dealing with antibiotics, but there is no use laboring the subject.

One of the outstanding features of the book is the detailed bibliography which fairly well covers the pharmacological literatures since January 1, 1940. The book is well printed and well bound. If it were not for the fact that the reader cannot have full confidence in its accuracy where new drugs are concerned, it would be a valuable addition to the physician's library.—*J.D.R.*

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*A Visit to the Hospital. By Francine Chase under supervision of Lester L. Coleman, M.D. Illustrated by James Bama. Published by Grosset and Dunlap, Inc., New York. 68 pages. Price $1.50.*

This children's book is an account of a boy, Stevie, who goes to the hospital for a tonsillectomy. It simply but effectively describes the clinical examinations, the anatomy, and the reasons for the operation, the various admitting procedures and environment of the hospital room and surgery. It depicts the various steps of the operation, the anesthesia, the convalescent phase.

The text can be read by a child with third grade reading ability. For younger children, there are efective drawings which parallel the content of the text and can be easily followed as an adult reads the story. Several children were asked to read this book, and all indicated their pleasure with it. One little boy, who had recently had a tonsillectomy, immediately identified with the entire narrative.

This is the type of consideration for a child's feeling and the type of preparation for what, to some children, may be a mysterious ordeal, that is most necessary in our present enlightened medical era. It would be a hope that one of the things the book can accomplish would be to bring to the attention of adults how important it is to prepare and to share with the child such a major life adventure.—*H.G.G.*

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*The Ciba Collection of Medical Illustrations, Volume III. Digestive System, Part III, Liver, Biliary Tract, and Pancreas. By Frank H. Netter, M.D. Commissioned and Published by Ciba Pharmaceutical Products, Inc. Price $10.50.*

In publishing a review of the above named book in its July issue, the JOURNAL inadvertently quoted the price as $13 instead of the correct figure, $10.50. The change is noted here so that those who were influenced to purchase the book from the favorable review will know the correct amount.

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*Surgery: Principles and Practice. Edited by J. Garrott Allen, Henry N. Harkins, Carl A. Moyer, and Jonathan E. Rhoads. Published by J. B. Lippincott Company, Philadelphia. 1,495 pages. Price $16.*

One might well ask why another textbook of surgery should be put on the market when so many satisfactory volumes are already available. This one, however, seems to be on a somewhat different basis—emphasizing "physiological, biochemical, pathologic, and anatomic bases of surgical practice"—and hoping that it would improve the background knowledge of medical students for good surgical practice.

The opening chapter—"Surgical Philosophy"—is thought-provoking reading for anyone, and it and the chapter on "Wound Healing" are worthy of the time of the experienced as well as the student surgeon.

The book emphasizes "the things that most doctors need to know about surgery rather than the more detailed points of technic that the surgeon uses," yet as an example of principle it contains detailed descriptions of some of the important procedures. Contemporary surgery is featured prominently, and all the surgical specialties (except ophthalmology and otolaryngology) receive recognition in the text.

It is a good text, well written, with good illustrations, and it deserves a place in our surgical libraries, as well as in those of the medical students.—*O.R.C.*

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*Surgery in World War II, Orthopedic Surgery, European Theater of Operations. Published by Office of the Surgeon General, Department of the Army, Washington, D. C.*

This book is one of the series being published by the Medical Department of the U. S. Army relating experiences in caring for the wounded during World War II. It is a systematic presentation of the various facets of hospital function—administration, training, an explanation of the "consultant system," facilities available and how they were used, principles of mass management of casualties, and experiences of representative hospitals in the theater of operations. There is also a detailed (and still concise!) presentation of principles of treatment of specific types of injuries, with the why and wherefore of failure or success. This may sound like dull reading; actually it is nothing of the sort, and for anyone who had a part in its making there is constant anticipation in its reading. One may ask, "Why any interest in such a history of war surgery 11 or 12 years after it is over?" For doubting Thomases good reason is given in the introduction. During World War I a few British and American surgeons had, after the unsatisfactory consequences of primary wound closures, evolved a plan of management including adequate debridement and delayed closure, which achieved satisfactory results "in more than 80 per cent of the wounds in which they were employed." However, the "American orthopedic experience was relatively brief . . . limited to a relatively small number of highly competent, top-ranking officers . . . not relayed to the outlying and forward hospitals. . . .

"This priceless information was incorporated in both the British and American official histories of the medical experience in World War I. It would have proved extremely valuable had it been put to immediate use in World War II. It was not. Almost no use was made of these techniques in the interim between the wars. They were not utilized when World War II broke out, either in the training of medical officers after it had become evident that United States participation in the war was inevitable, or later, when this country entered the war.

"If the medical histories of World War II incorporate the clinical experiences of that war and if what is printed will be read in the future—as it has not always been read in the past—military surgeons will not, in the future, repeat the mistakes of the past as they did in World War II."

We don't want another war experience, but if we must have one we can learn from the vast experiences of World War II, and much of it is also applicable to civilian surgery—particularly the care of mass casualties.

Two additional volumes are planned on orthopedic surgery. It will be an excellent treatise if they follow the standard of this volume.—*O.R.C.*

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*Surgery in World War II. General Surgery, Volume II. Edited by Col. John Boyd Coates, Jr., MC; Michael E. DeBakey, M.D.; W. Philip Giddings, M.D., and Elizabeth M. McFetridge, M.A. Pub-*

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***References:*** 1. Borrus, J. C.: *M. Clin. North America,* In press, 1957. 2. Gillette, H. E.: *Internat. Rec. Med. & G. P. Clin.* 169:453, 1956. 3. Pennington, V. M.: *J.A.M.A.,* In press, 1957. 4. Cayer, D.: Prolonged Anticholinergic Therapy of Duodenal Ulcer. Am. J. Dig. Dis. 1:301-309 (July) 1956. 5. McGlone, F. B.: Personal Communication to Lederle Laboratories. 6. Texter, E. C., Jr.: Personal Communication to Lederle Laboratories. 7. Bauer, H. G. and McGavack, T. H.: Personal Communication to Lederle Laboratories.

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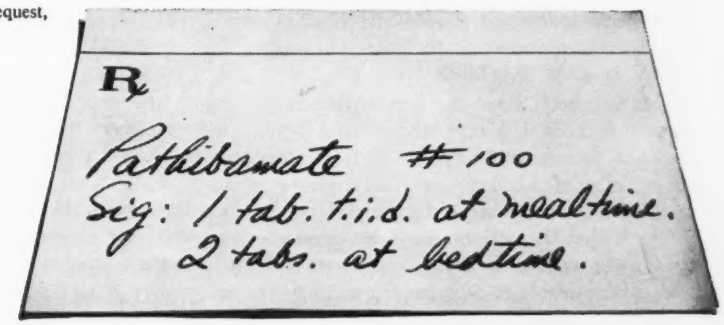


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*lished by Office of the Surgeon General, Department of the Army, Washington, D. C. 417 pages. Price $4.25.*

This is another of the series being published by the Medical Department of the U. S. Army. Although called Volume II, this is the first of the series on general surgery.

The principal subject of the volume relates to experiences in care of abdominal injuries encountered by the Second Auxiliary Surgical Group, operating within the Mediterranean theater. The fact that 3,154 abdominal injuries and 839 thoracoabdominal injuries were encountered is impressive, but the details of information which were preserved, even during periods of the stress of military surgery, make this document more useful than many might expect. The vast experiences justify conclusions, and the conclusions justify careful consideration of other surgeons.

The problems of the severely (or critically) injured are discussed, beginning with the moment of the patient's admission to a forward field hospital. Resuscitation, control of pain, and anesthesia are all important and are given due credit for their share of the successful care of these severely injured soldiers. The main body of the book deals with injuries to each of the organs within the abdomen, and a closing division presents the problem of colostomy as related to abdominal trauma—a vastly different concept from that extant before the related experience.

With the consideration of complications and factors of mortality, and a summary of conclusions drawn from the experiences, there is much to be learned from such a compilation of facts.—*O.R.C.*

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*The Physician-Writer's Book—Tricks of the Trade of Medical Writing. By Richard M. Hewitt, M.D. Published by W. B. Saunders Company, Philadelphia. 415 pages, 37 figures. Price $9.00.*

"The aim in preparing the book was to aid the inexperienced, inexpert, occasional physician-author, whose material is written for other physicians. The volume is not a style book."

This is a book about the organization and preparation of medical papers, theses, and books. All phases of the problem are considered, from the original decision of whether one "has anything to say" to the final conclusions and titling of the product.

The author is well qualified by experience and training to write such a book. Much which is in it would be valuable to all who are writing even one paper, but obviously not all such authors would (or could) read it.

There is a consideration of the production of the article or book first as a whole, then by paragraphs, and finally as sentences. Any physician would learn to read more objectively after reading or scanning this book. For one who is contemplating writing a book or thesis or a number of papers, invaluable help would be obtained.

The book is interesting reading; it is printed with clear type and good format; there is much valuable information. The only drawback is that so few are apt to read it, since they will feel they do not need a book on medical writing. It is deserving of a wider distribution than it will probably get.—*O.R.C.*

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*Fluid and Electrolytes in Practice. Second Edition. By Harry Statland, M.D. Published by J. B. Lippincott Company, Philadelphia. 229 pages. Price $6.00.*

This is a dandy book for the clinician who is faced with fluid and electrolyte balance problems. Though not a comprehensive treatise, this volume is packed full of valuable information. Data are well presented in a clear easy to read style. Each sentence is direct and terse. The author has done a remarkable job in putting a maximal amount of information in a minimal number of words. The book is intended primarily as a teaching primer and is just that. Discussion of controversial experimental data has been avoided. Numerous diagrams are used advantageously to supplement the text.

The book is divided into two sections. The first deals with basic principles of fluid movement and major abnormalities of volume, concentration, and acid-base balance. The problems presented by various surgical situations are also dealt with in this section. The second section discusses fluid and electrolyte disturbances in various clinical conditions such as heart disease, kidney and urologic disease, diabetic acidosis, burns, cirrhotic ascites, and toxemia of pregnancy. There is also a discussion of pediatric fluid balance. The sections dealing with potassium metabolism and its excretion have been largely rewritten. The role of ADH in the posttraumatic state has been stressed. A discussion of salicylism has been added to this edition.

Although some of the discussions in various clinical states are necessarily on the brief side, the reader is presented with a bibliography of over 200 references from which he can get further information on a given subject.

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This volume is a valuable addition to any physician's library since it is the type of book that one will want to reread periodically.—*W.G.C.*

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*Regulation and Mode of Action of Thyroid Hormones. Ciba Foundation Colloquia on Endocrinology, Volume X. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Published by Little, Brown and Company. 309 pages. Price $8.50.*

This collection of 18 very technical papers represents the most recent thinking about the regulation and mode of action of the thyroid hormones. The papers themselves are much too involved to be of interest to most medical readers, but the discussions following each paper are more readable and contain all the pertinent points. The subjects discussed are as indicated by the title of the book and in themselves represent summaries of the present thinking along those lines. All in all, this is a good reference book about this aspect of thyroid physiology.—*J.W.S.*

# ANNOUNCEMENTS

Twenty-second annual congress, U. S. and Canadian Sections, International College of Surgeons, Palmer House, Chicago, September 8-12. Three-day program on surgical problems of eye, ear, nose, and throat, beginning September 9. Section on Plastic and Reconstructive Surgery, beginning September 9.

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Twenty-second annual meeting, Mississippi Valley Medical Society, Sheraton-Jefferson Hotel, St. Louis, September 25-27. Panel discussions on burns, obstetrics, acute surgical abdomen, peptic ulcer, pediatric chronic diseases, headache. All A.M.A. members invited. Write Secretary, 209 W.C.U. Building, Quincy, Illinois.

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Clinical congress, American College of Surgeons, Atlantic City, October 14-18. Information available from College, 40 East Erie Street, Chicago 11, Illinois.

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Fourth annual meeting, Academy of Psychosomatic Medicine, October 17-19, Morrison Hotel, Chicago. Program on "Psychosomatic Aspects of Obstetrics, Gynecology, Endocrinology and Diseases of Metabolism." Secure information from Secretary, 104 South Michigan Avenue, Chicago 3, Illinois.

Three postgraduate courses on diseases of the chest offered by American College of Chest Physicians, (1) Hotel Knickerbocker, Chicago, October 21-25; (2) Park-Sheraton Hotel, New York City, November 11-15; (3) Ambassador Hotel, Los Angeles, December 9-13. Tuition $75. Write Executive Director, 112 East Chestnut Street, Chicago 11, Illinois.

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Orthopedic fellowships for advanced training in teaching or research available from National Foundation for Infantile Paralysis, 301 East 42nd Street, New York 17, New York. Applications received from physicians eligible for board certification until September 1.

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## Ureteral Injury

*(Continued from Page 512)*

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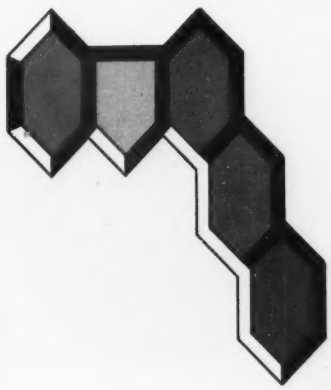

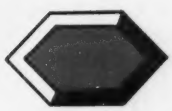

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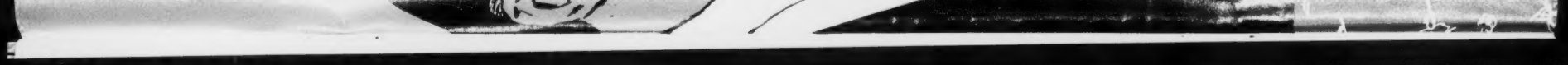

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# ABSTRACTS FROM CURRENT LITERATURE

## Mentally Afflicted Children

*Goldstein, Hyman: Physical therapy and rehabilitation for mentally afflicted children, Arch. Ped. 73:9, 321-337 (Sept.) 1956.*

Mentally afflicted children are the end result of vast variety of etiological factors. About 60 per cent of these children are mentally retarded and 40 per cent, approximately, have epileptic seizures. If proper treatment is given, many of these children are markedly improved both physically and emotionally.

Cortical lesions occur in about 65 per cent, resulting in the spastic form of cerebral palsy. The choreiform-athetotic type occurs in 20 per cent of the children, a lesion in the basal ganglia. A tremor type has similar origin and is found in 2 per cent of the cases. The ataxic form occurs in 8 per cent. There are about 500,000 cerebral palsied children in the United States, and thousands of new patients are born each year.

Treatment: The physical therapy or training period for the cerebral palsied child is a long, slow, and tedious one. There are 15 modalities for the treatment of all types of cerebral palsy: massage, passive motion, active assisted motion, active motion, resisted motion, conditioned motion, automatic or confused motion, combined motion, rest, relaxation, motion from relaxed position, balance, reach and grasp, reciprocation, skills.

The children may need medical aid of many types during their periods of physical training, including anticonvulsants, tranquilizers, endocrines, vitamins, mineral supplements, and dietetic regulations. Hearing and vision disturbances must be corrected. Educational and vocational guidance and training develop a better personality, independence, and social maturity.—*D.R.D.*

---

## Juvenile Diabetes

*Brown, Edward E.: Infectious origin of juvenile diabetes, Arch. Ped. 736, 191-198 (June) 1956.*

The history of onset of diabetes is easier to trace in children than in adults. There is considerable evidence that infection may cause diabetes.

History of diabetes preceded by infection is common. Various authorities report the following incidence of infection preceding juvenile diabetes: Joslin 15 per cent; Landabura and Magdalena 23 per cent; Toverud 26 per cent; John 32.8 per cent; Fischer 35 per cent; Boyd 56.2 per cent; White 98 per cent, and Friese and Jahr 75 per cent.

The more common infections are measles, scarlet fever, varicella, mumps, influenza, pertussis, pneumonia, acute coryza, acute tonsillitis, and sinusitis. The interval following infection and diabetes developing varies from 10 to 30 days.

Diabetic coma following infection is frequently the time of initial diagnosis of diabetes. Onset of diabetes is more common during the stormy months of the year. Usually improvement occurs during summer months. The pancreas seems to have much more ability to regenerate when the toxic assault upon it is most minimal.

The highest incidence of diabetes exists in climates where streptococcic infections are more prevalent. There is a much higher diabetic death rate in temperate than in tropical climates.

Sinusitis, in the author's opinion, is the most common antecedent infection. Chronic tonsillitis and sinusitis are common in juvenile diabetes.

Diabetic children usually have increased sedimentation rates and increased capillary fragility. Darschner and his co-workers reported that 90 per cent of diabetics with increased capillary fragility also had retinopathy. Chronic sinusitis, elaborating streptococcus toxins, is a frequent focus for both retinitis and nephritis.

Pathologically, John found definite pancreatic changes in about 96 per cent of children. Most show hydropic degeneration of the Isles of Langerhans, resulting in hypofunction. The beta cells in the islets, containing granules which are precursors of insulin, are usually partially or completely degranulated. This condition is also found in experimental diabetes in rats.

The strong persistence of the diabetic state may well be due to the continuous prolonged attack of toxins on the pancreas. Penicillin therapy has favorably influenced the prognosis in infantile diabetes.

The heredity factor is found in from 25 to 40 per cent. Although infection seems to be the most common precipitating cause, it is impossible to demonstrate bacterial toxins in blood or in the pancreas. It seems similar to the arthritic manifestations of streptococcus infections. Streptococcus toxins injure not only the pancreas; they also affect pituitary and other endocrine glands.

Rheumatic children, both diabetic and non-diabetic, and children with chronic infections, show a high incidence of diabetic-type glucose tolerance curves. Some of these children become diabetic after an acute infection, or after continuing low grade infection. Treatment of acute upper respiratory infections, chronic sinusitis, tonsillitis, and other foci of infec-

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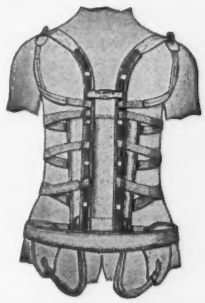

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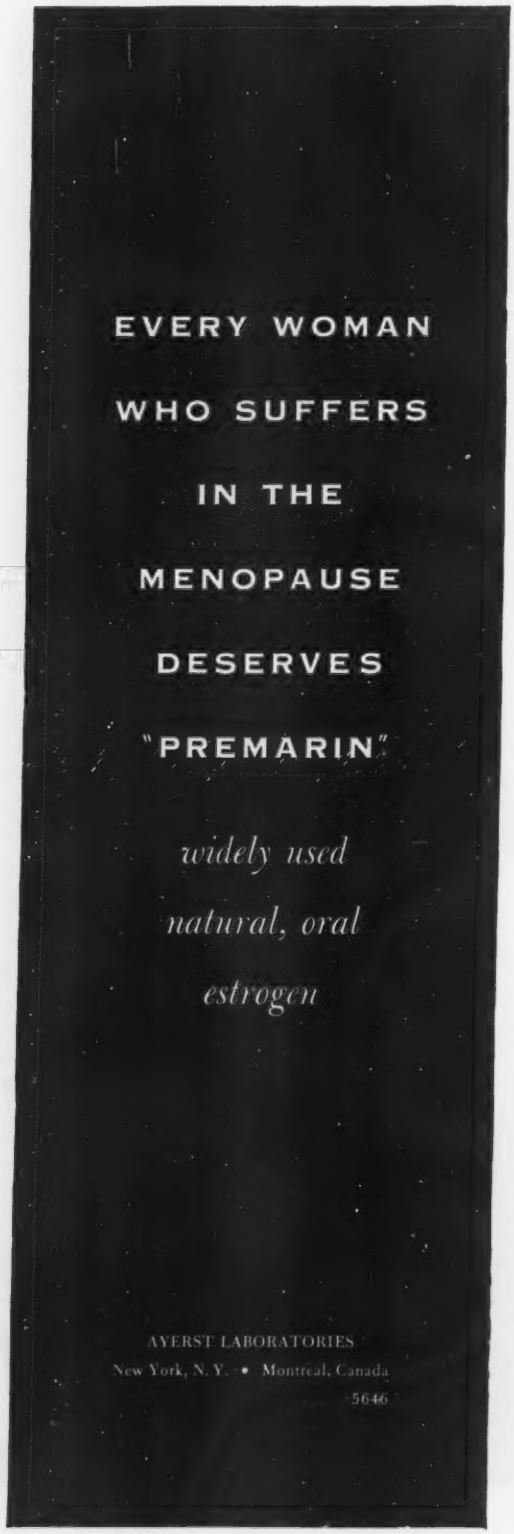


tion may help to prevent diabetes and its complications. Children should have weekly urine examinations for five or six weeks following such an infection. Such complications as retinitis seem to be related to the duration of diabetes rather than the adequacy of treatment regime. Persistence of chronic infection may account for the complications, e.g. chronic sinusitis.

Juvenile diabetes may be prevented largely by control and adequate treatment of childhood infections.—*D.R.D.*

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### Periodic Health Appraisal of Children

A new program endorsing periodic health appraisal for children, sponsored by the National Congress of Parents and Teachers, has won support of the A.M.A.'s Council on Medical Service. At a recent meeting the Council voted to approve the following resolution: "The Committee on Maternal and Child Care of the Council on Medical Service, A.M.A., reaffirms its approval of the principle of continuous health supervision of children from birth through their school experience rather than only a program of a single appraisal on school entrance. It also recommends that, where possible, this should be done by the physician and dentist who normally serve that child and family, preferably his personal physician and dentist. The committee welcomes the support of the National Congress of Parents and Teachers."

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### Guides on Voluntary Agencies

A new "Guides to Relationships Between Medical Societies and Voluntary Health Agencies" has been published by the American Medical Association. Prepared by the Committee on Relationships between Medicine and Allied Health Agencies, the booklet points up the nature of voluntary health agencies, the questions that need to be answered in evaluating such agencies, and the medical society's obligations to voluntary agencies, and the voluntary agency's obligations to the medical society.

Last fall the committee issued a brief outline on this subject which stimulated such interest among medical societies that the more detailed and comprehensive set of guides was prepared. Copies may be secured from the Council on Medical Service.

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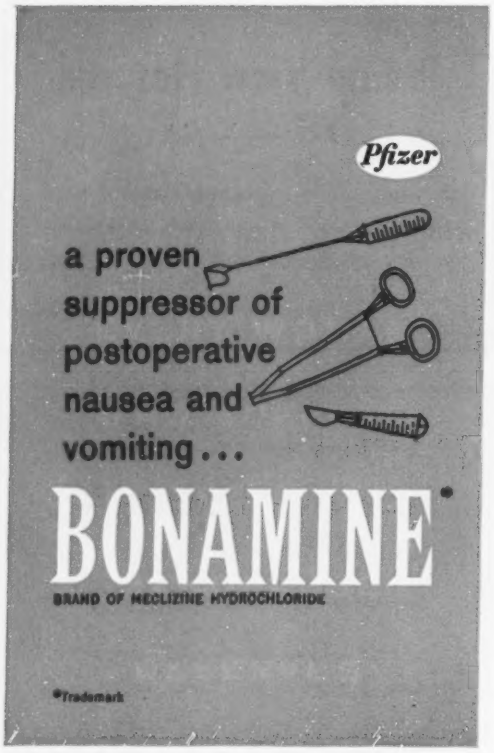

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